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ARTICLE

Social status and demographic effects of the kappa opioid receptor: a PET imaging study with a novel agonist radiotracer in healthy volunteers

David Matuskey[1,2,3], Mark Dias[1], Mika Naganawa[1], Brian Pittman[2], Shannan Henry[1], Songye Li[1], Hong Gao[1], Jim Ropchan[1], Nabeel Nabulsi[1], Richard E. Carson[1] and Yiyun Huang[1]

Kappa opioid receptors (KORs) have been characterized as an aversive system in the brain and implicated in social behavior in preclinical models. This work investigated the effect of social status on the KOR system in humans using positron emission tomography (PET) imaging with the novel KOR agonist radiotracer [^{11}C]EKAP. Eighteen healthy participants (mean age 41.2 ± 9.3) completed the Barratt Simplified Measure of Social Status (BSMSS), an MRI and an [^{11}C]EKAP PET scan on the High Resolution Research Tomograph. Arterial blood sampling and metabolite analysis were conducted to obtain the input function. Regions of interest were based upon an MR template and included the reward/aversion areas of the brain. The multilinear analysis-1 (MA1) method was applied to the regional time-activity curves (TACs) to calculate [^{11}C]EKAP regional volume of distribution (V_T). Mixed models and Pearson correlation coefficients were used for body mass index (BMI), gender and age, with age being dropped in subsequent analyses because of nonsignificance. An overall effect of primary ROIs ($F_{7,112}$ 7.43, $p < 0.0001$), BSMSS score ($F_{1,13}$ 7.45, $p = 0.02$), BMI ($F_{1,13}$ 23.5, $p < 0.001$), and gender ($F_{1,13}$ 23.75, $p < 0.001$), but not age ($F_{1,13}$ 1.12, $p = 0.35$) was observed. Regional [^{11}C]EKAP V_T and BSMSS were found to be negatively correlated in the amygdala ($r = -0.69$, $p < 0.01$), anterior cingulate cortex ($r = -0.56$, $p = 0.02$), caudate ($r = -0.66$, $p < 0.01$), frontal cortex ($r = -0.52$, $p = 0.04$), hippocampus ($r = -0.60$, $p = 0.01$), pallidum ($r = -0.59$, $p = 0.02$), putamen ($r = -0.62$, $p = 0.01$), and ventral striatum ($r = -0.66$, $p < 0.01$). In secondary (non-reward) regions, correlations of [^{11}C]EKAP V_T and BSMSS were nonsignificant with the exception of the insula. There was an inverse correlation between social status and KOR levels that was largely specific to the reward/aversion (e.g., saliency) areas of the brain. This finding suggests the KOR system may act as a mediator for the negative effects of social behaviors in humans.

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INTRODUCTION

Kappa opioid receptors (KORs) are the most abundant opioid receptors in the brain [1] with widespread distribution in areas highly linked to stress and reward [2–4]. Unlike the reinforcing mu (MOR) and delta (DOR) opioid receptors [1], KOR has high selectivity for endogenous dynorphins (as opposed to enkephalins) [5] and stimulation of KORs are aversive, sometimes referred as an "anti-reward" or stress system [6, 7]. The stimulation of KOR can also decrease dopamine release in the brain and therefore is a counterbalance to reinforcing properties of MOR, DOR, and dopamine [8, 9].

Multiple lines of evidence implicate KOR activity during stress (mediated by dynorphins) [10–13] and in maintenance of addiction through a negative reinforcement cycle of dysphoria, irritability, anxiety, anhedonia, malaise, emotional pain, and loss of motivation for natural rewards when abstinent [7, 14–16]. Recent findings have suggested a major component of natural rewards, social experiences, are also affected by KORs [17, 18]. KOR activation influences social behavior in rodents, decreasing social play while antagonism appears to reduce animal reactions to distressing social stimuli [17, 19, 20]. Mice given a KOR antagonist, or lacking a gene for dynorphin (i.e., *Pdyn)*, did not show a typical defeated posture after exposure to repeated social defeats compared with placebo animals [21]. In the nucleus accumbens, an area integral to rewards, KOR-mediated social aversion in prairie voles [22], social status in starlings [23], and in rats there was an upregulation with social isolation [12]. Susceptible and resilient animals have also shown different expression levels of dynorphin mRNA in response to social stressors [24, 25], although differences have also been reported in this region and others [26].

The current work focuses on translating findings from animal studies implicating the KOR in social phenomena into humans by using positron emission topography (PET) imaging with the novel KOR agonist tracer [^{11}C]EKAP [27]. This provides the first in vivo examination in humans of the relationship between KOR and social status.

PARTICIPANTS AND METHODS

Participants

This study was performed under protocols approved by the Yale Human Investigation Committee, Yale University Radiation Safety

[1]Department of Radiology and Biomedical Imaging, Yale University, New Haven, CT, USA; [2]Department of Psychiatry, Yale University, New Haven, CT, USA and [3]Department of Neurology, Yale University, New Haven, CT, USA
Correspondence: David Matuskey (david.matuskey@yale.edu)

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Committee, Yale-New Haven Hospital (YNHH) Radiation Safety Committee, and Yale MRI Safety Committee. Eighteen healthy subjects without a history of psychiatric disorders or substance abuse were studied. Other exclusion criteria were current or past serious medical or neurological illness (e.g., history of head injury with loss of consciousness), current pregnancy (as documented by pregnancy testing at screening and on the day of the PET imaging study), breast feeding, or contraindications to magnetic resonance imaging (MRI). Subject eligibility was confirmed by comprehensive medical and psychiatric histories, physical examination, neurological and mental status exam, routine laboratory studies, electrocardiogram, and semi-structured [28] or structured clinical interview [29].

Once eligible, subjects completed the Barratt Simplified Measure of Social Status (BSMSS) [30]. The BSMSS has been used in previous work with PET [31, 32] and is a comprehensive and updated measure of social status based on the Hollingshead index [33]. The BSMSS generates a single comprehensive total score of social status taking into account the education and occupation of the participants, their parents, and their spouse. The total score of the BSMSS was used in the analyses and it is weighted to favor the scores of the research participants and significant others over that of the parents. All screening records (e.g., occupation and education) on intake were reviewed to confirm an accurate BSMSS report.

Participants were recruited from the greater New Haven area by advertisement, word of mouth, and referral. Informed consent was obtained from all participants after a thorough explanation of the study procedures.

Radiochemistry, scanning, and imaging procedures

[^{11}C]EKAP was prepared as previously reported [27, 34]. ^{11}C-EKAP displays faster kinetics and better test–retest reproducibility than the first-generation KOR agonist radiotracer ^{11}C-GR103545 (known as ^{11}C-MKAP at our center), and good specific binding signals in vivo [35]. Average (SD) injected mass dose was 0.014 (0.004) µg/kg and specific activity was 261.8 (111) MBq/nmol at the time of injection.

All subjects received a structural MRI scan on a 3-T Trio system (Siemens Medical Solutions, Malvern, Pennsylvania) with a circularly polarized head coil for purposes of excluding individuals with structural abnormalities and anatomically co-registering with the PET images. The dimension and voxel size of MR images were $256 \times 256 \times 176$ voxels and $0.98 \times 0.98 \times 1.0$ mm^3, respectively.

Each subject then received a 120 min PET scan with [^{11}C]EKAP on the High-Resolution Research Tomograph (HRRT) (Siemens/CTI, Knoxville, TN, USA) with 207 slices (1.2 mm slice separation) and a reconstructed image resolution of ~3 mm. A transmission scan with a ^{137}Cs point source was obtained for attenuation correction before the emission scan.

Motion correction was based on an optical detector (Vicra, NDI Systems, Waterloo, Ontario, Canada). Dynamic PET scan data were reconstructed with all corrections (attenuation; normalization; scatter; randoms; deadtime and motion), using the MOLAR algorithm [36] with the following frame timing: 6×30 s; 3×1 min; 2×2 min; 22×5 min.

A summed image (0–10 min after injection) was created from the motion-corrected PET data and registered to the subject's MR image, which in turn was nonlinearly registered to a MR template (Montreal Neurological Institute space). All transformations were performed with Bioimagesuite (version 2.5; http://www.bioimagesuite.com).

Primary regions of interest (ROIs) included the reward/aversion areas of the amygdala, anterior cingulate cortex (ACC), caudate, frontal cortex, hippocampus, pallidum, putamen, and ventral striatum (VS) and were based on the Anatomical Automatic Labeling (AAL) template delineated on MR with the exception of a hand-drawn VS template as done in prior work [37, 38]. A post-hoc test was also done in frontal cortex subdivisions including the ventromedial prefrontal cortex (vmPFC), orbitofrontal cortex (OFC) and dorsolateral prefrontal cortex (dlPFC). Secondary areas included non-reward areas of the thalamus, insula and parietal, temporal and occipital cortical regions. The cerebellum had relatively low KOR binding (mean $V_T = 5.7$), was not significant and excluded from further analysis.

Arterial blood sampling and metabolite analysis were conducted during each PET scan to obtain the arterial input function. The multilinear analysis-1 (MA1) method was applied to the regional time-activity curves (TACs) to calculate [^{11}C]EKAP volume of distribution (V_T) using the metabolite-corrected input function.

Statistical considerations

All outcomes were summarized descriptively and assessed for normality prior to analysis using normal probability plots and Kolmogorov test statistics. All outcomes were approximately normal. Linear mixed models were used to examine the independent and joint effects of group (between-subject factor) and region of interest (within-subject factor) on V_T values. Within-subject correlations were accounted for by fitting three variance–covariance structures to the data (unstructured, compound symmetry, and heterogeneous compound symmetry) with an unstructured form fitting the data best according to the Bayesian Information Criterion (BIC). Gender, age, body mass index (BMI), and injection mass dose were considered as covariates in the above models but age and injection dose were not significant and dropped for parsimony. Potential associations between BSMSS scores, clinical characteristics, and demographics with ROIs were estimated using Pearson correlation coefficients and subsequently adjusted for BMI and gender due to known effects of these variables on KOR [39]. Given the interrelation of the primary ROIs, a Hommel-adjusted p-value was selected. All analyses were considered significant at the two-tailed $\alpha < 0.05$ threshold and were conducted using SAS, version 19 (Armonk, NY).

RESULTS

Means and standard deviations of demographic and clinical characteristics for the participants are shown in Table 1. All subjects were nonsmokers and had no or minimal current weekly alcohol consumption (up to three drinks per week).

The results of the primary mixed model showed significance for an overall effect of primary ROIs ($F_{7,112}$ 7.43, $p < 0.0001$), BSMSS score ($F_{1,13}$ 7.45, $p = 0.02$), BMI ($F_{1,13}$ 23.5, $p < 0.001$), and gender ($F_{1,13}$ 23.75, $p < 0.001$), but not a significant social status–ROI interaction ($F_{1,13}$ 1.14, $p = 0.34$) or overall effect of age ($F_{1,13}$ 1.12, $p = 0.35$). Age was subsequently dropped from further model analyses. BSMSS was not significantly different between genders (mean total score was 58 for males and 61 for females). BSMSS was also not correlated with age ($r = -0.12$, $p = 0.96$) or BMI ($r = -0.15$, $p = 0.55$); correlations for both age and BMI and all ROIs are in Table 2. Gender differences for ROIs are also presented in Table 3.

Table 4 presents average V_T values (with standard deviations) for the primary ROIs along with correlations after being adjusted for BMI and gender with uncorrected p-values, the slope of the BSMSS and V_T values corrected for multiple comparisons. Individual data points are shown in Fig. 1 for BSMSS total score

Table 1. Age, BMI, and BSMSS values are mean (SD)

Age	Gender	Race	BMI (kg/m^2)	BSMSS
35 (10); range 20–51	9M, 9F	8C, 6 AA, 3O,1H	26 (3); range 20–31	60 (18); range 22–87

For race, *C* Caucasian, *AA* African-American, *O* Other, *H* Hispanic

Table 2. Age and BMI correlations with all ROIs

ROI	Age	*p*-Value	BMI (kg/m^2)	*p*-Value
Amygdala	−0.2975	0.23	−0.5438	0.02
ACC	−0.2478	0.32	−0.4753	0.05
Caudate	−0.4399	0.07	−0.6944	<0.001
Frontal cortex	−0.3904	0.11	−0.7266	<0.001
Hippocampus	−0.3067	0.22	−0.6300	<0.01
Occipital cortex	−0.4074	0.09	−0.7156	<0.001
Pallidum	−0.3485	0.16	−0.6391	<0.01
Parietal cortex	−0.4422	0.07	−0.6986	<0.01
Putamen	−0.4044	0.10	−0.7362	<0.001
Temporal cortex	−0.3854	0.11	−0.7400	<0.001
Thalamus	−0.4137	0.09	−0.7055	<0.01
VS	−0.4096	0.09	−0.6607	<0.01

The *p*-values are uncorrected for multiple comparisons

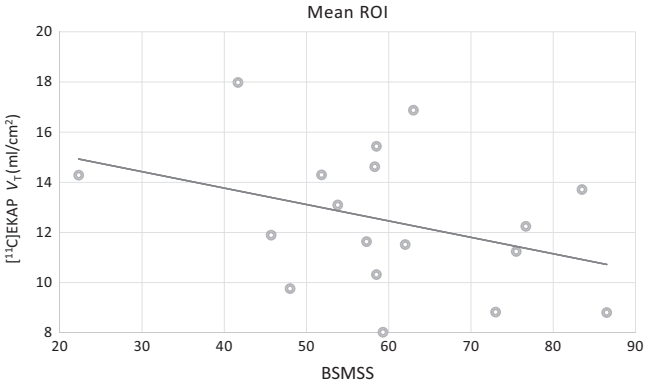

Fig. 1 Mean region of interest (ROI) includes all the primary ROIs along with the total Barratt Simplified Measure of Social Status (BSMSS) score. Values shown are unadjusted for body mass index (BMI) and gender

Table 3. Gender differences between ROIs

	Males			Females					
	N	Mean	Std dev	*N*	Mean	Std dev	DF	*t*-Value	Pr > |t|
Amygdala	9	21.2	6.7	9	23.5	5.1	16	−0.86	0.40
ACC	9	13.4	2.6	9	16.0	3.2	16	−1.89	0.08
Caudate	9	6.7	1.5	9	9.2	1.8	16	−3.26	<0.01
Frontal cortex	9	8.6	1.5	9	11.0	1.7	16	−3.26	<0.01
Hippocampus	9	7.8	1.7	9	9.5	2.1	16	−1.89	0.08
Insula	9	13.0	2.6	9	16.9	2.7	16	−3.09	0.01
Occipital cortex	9	7.3	1.3	9	9.3	1.1	16	−3.48	<0.01
Pallidum	9	10.4	2.0	9	14.2	3.3	16	−2.98	0.01
Parietal cortex	9	7.6	1.3	9	9.7	1.3	16	−3.46	<0.01
Putamen	9	8.7	1.4	9	11.4	2.0	16	−3.38	<0.01
Temporal cortex	9	9.3	1.7	9	11.7	1.7	16	−3.12	<0.01
Thalamus	9	4.5	0.7	9	5.8	0.9	16	−3.47	<0.01
VS	9	12.1	2.6	9	15.9	3.0	16	−2.88	0.01

T-test was used between groups for each ROI. The *p*-value is two-sided and uncorrected for multiple comparisons

Table 4. V_T values are mean (SD) and shown with correlation with BSMSS total score after being adjusted for BMI and gender

Region of interest (ROI)	V_T mean (SD)	Pearson *R*	*p*-Value	Slope	*p*-Value (Hommel)
Amygdala	22.4 (5.9)	−0.69	<0.01	−0.1963	0.04
ACC	14.7 (3.1)	−0.56	0.02	−0.0892	0.04
Caudate	7.9 (2.1)	−0.66	<0.01	−0.0493	0.03
Frontal cortex	9.8 (2.0)	−0.52	0.04	−0.0353	0.04
Hippocampus	8.7 (2.0)	−0.60	0.01	−0.0579	0.04
Pallidum	12.3 (3.3)	−0.59	0.02	−0.0733	0.04
Putamen	10.1 (2.1)	−0.62	0.01	−0.0432	0.04
VS	14.0 (3.4)	−0.66	<0.01	−0.0817	0.04

The slope of the BSMSS value is also shown in each primary region along with corrected *p*-values

and an averaged unadjusted value of the primary ROIs. Individual ROIs are shown in supplemental Figure S1. A post-hoc test of frontal cortex subdivisions showed correlations in the vmPFC ($r = -0.55$, $p = 0.03$), OFC ($r = -0.48$, $p = 0.06$), and dlPFC ($r = -0.52$, $p = 0.04$).

The secondary non-reward areas were nonsignificant with BSMSS score in the thalamus ($r = -0.32$, $p = 0.22$), parietal ($r = -0.36$, $p = 0.18$), temporal ($r = -0.47$, $p = 0.07$), and occipital cortical regions ($r = -0.39$, $p = 0.13$), with the exception of the insula ($r = -0.58$, $p = 0.02$). These values were adjusted for BMI and gender, but not multiple comparisons. Representative images of individuals with the highest and lowest BSMSS scores are shown in Fig. 2 for comparison purposes.

DISCUSSION

The current study is the first to directly investigate the relationship between the KOR system and social status in humans. Using a novel KOR tracer, we found an inverse correlation between social

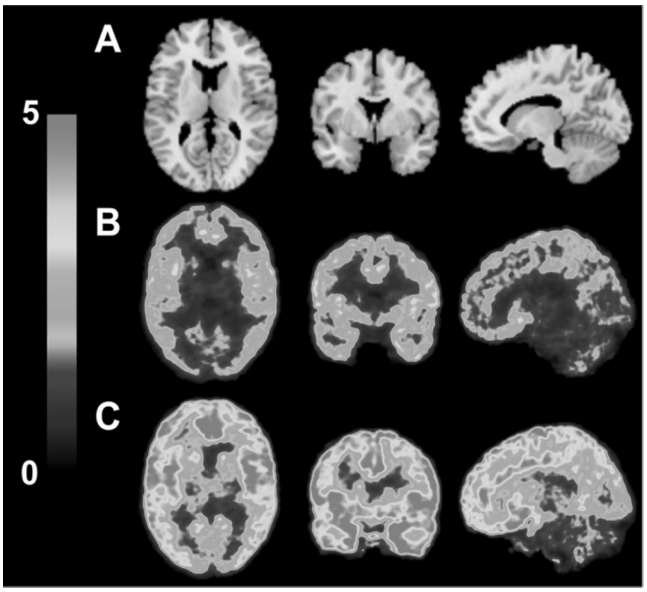

Fig. 2 Template MR (**a**) and co-registered positron emission tomography (PET) images summed from 30 to 90 min after 11C-EKAP injection for high (**b**) and low (**c**) Barratt Simplified Measure of Social Status (BSMSS) score individuals. Activity is expressed as SUV [concentration/(injected dose/body weight)]

status and KOR levels that was largely specific to the primary ROIs. This relationship gives evidence that lower social status in humans is associated with increased KOR levels, which is important because these regions are implicated in the "anti-reward"/stress systems and are at least partially mediated by dynorphins/KOR in the brain [6, 7]. The robust V_T values (7.9–22.4) also provide support for the importance of KOR in these areas.

With lower social status viewed as a stressor, our findings of increased KOR levels largely fit with the extant animal literature on social processes, and more exactly, with the lone study on social status and KOR (in male European starlets) [23]. Pair bonding, an important social behavior, has been more studied and found to be influenced by KOR in monogamous animals such as titi monkeys and prairie voles [40–42]. Factors such as these could presumably influence social status across species. In humans, there is less evidence of KOR impacted by social processes, but indirect suggestion with pharmacologic studies is available. One double-blind, placebo-controlled study in 48 healthy controls found evidence that low-dose buprenorphine, a KOR antagonist/MOR agonist, diminishes the response to social stress in behavioral tasks [43]. Naltrexone, a nonspecific opioid antagonist, has also been found to alter emotional reactions to social stimuli, with the authors speculating that increased attention to emotional expression, slowed identification of sadness and fear, and decreased ratings of arousal for social and nonsocial emotional scenes were more consistent with KOR rather than MOR antagonist effects [44]. Both of these studies were not designed to tease out specific opioid receptor contributions, but more recent post-mortem work has attempted to do this in childhood abuse and control subjects. Opioid receptors (MOR, KOR, and DOR) were examined with real-time polymerase chain reaction in the ACC, mediodorsal thalamus, and anterior insula. Interestingly, only the KOR was found to be significantly different in controls, with downregulation in the anterior insula. It is not clear if these results are different from our own due to the type of stress or methodological differences [18]. Of note, the insula was included as a secondary region in the current analysis with similar findings as the primary regions, showing that anatomical variation is likely not the cause. A clinical PET imaging study at Yale in trauma-exposed subjects with no opioid use dependency showed a negative correlation between loss symptoms (i.e., emotional numbing, depression, and anxiety) and KOR availability in an composite brain region [45], congruent with our current findings and indicating that stress-related phenomena (either by social or trauma mechanisms) seem to be consistent in regards to the KOR in vivo.

The current findings do contrast, however, with previous work showing a positive correlation between striatal $D_{2/3}R$ availability and social status in humans using the non-selective $D_{2/3}R$ antagonist [^{11}C]raclopride [32, 46]. Our previous work showed a negative correlation in the substantia nigra/ventral tegmental area (SN/VTA) with the D_3R preferring $D_{2/3}R$ agonist tracer [^{11}C](+) PHNO [31], which is actually congruent with the [^{11}C]raclopride data considering the converse relationships of striatal D_2R and SN/VTA D_3R in other populations [38, 47–49]. Taken together, these studies in humans, as well as non-human primate studies [50] suggest an intricate relationship between dopamine function and social behavior where dopamine release and $D_{2/3}R$ may maintain social hierarchy [51]. The KOR system may be acting in opposing ways to the dopamine system as a mediator for the negative effects of social behaviors in humans. This possibility would have a direct mechanism to support it as physiologically KOR is located presynaptically on dopamine terminals and can suppress dopamine release in the reward areas of the brain [12, 52–54].

Like dopamine, MOR is also rewarding and has been implicated in social behavior in humans [55–57]. Imaging studies focused on social rejection indicate both increased and decreased MOR receptor availability with positive and negative social cues in healthy individuals [58]. The abundance of supporting evidence from animal literature [59, 60] makes it likely that MOR and dopamine systems are working in concert for the positive reinforcement of social behaviors, contrasting with the KOR system.

Previous work with an antagonist KOR tracer at Yale ([^{11}C] LY2795050) has shown gender differences with males having higher V_T than females across most brain regions [39]. The current findings are in the opposite direction (higher V_T in females than males) and given the similar methods a probable rationale for this difference is the use of a KOR agonist vs. antagonist tracer as the former might only detect a high affinity state while the latter could detect total KOR expression levels. There is literature to support possible agonist/antagonist differences, with females showing stronger clinical responses to KOR agonists than males [61–63]. Thus, in addition to showing a possible mechanism of gender-specific responses to pain and social aversion [20], these findings also highlight important considerations for the use of KOR agonist vs. antagonist tracers in future studies.

Statistically significant findings were also found with regards to BMI, with negative correlations (uncorrected) found in all regions with [^{11}C]EKAP V_T. While this is the first human report of a relationship between KOR and BMI, the KOR system has been implicated in eating disorders and obesity [64]. Higher concentrations of KOR have been found in obese compared with lean mice [65], and it's unclear why this differs from our findings although species and the selection of an agonist tracer likely have a role. In fact, KOR agonists and antagonists have both been found to augment eating behaviors with specific effects depending on species and paradigms [64, 66, 67]. Future studies could see if the current findings extend into morbid obesity and possibly beyond as KOR binding has been known to be altered in diabetic rats [68].

We did not observe any age effects in this cohort. This seems somewhat surprising considering that age effects on other neurotransmitter systems have been found by us and others with PET imaging [69–72], but the literature is noticeably quiet as to whether KORs are susceptible to aging with only a sole autoradiographic study of aging in guinea pigs finding

large decreases (18–42%) in cortical areas of 6- to 36-month-old animals [73].

Limitations of the current study include not being able to distinguish dynorphin receptor occupancy vs. KOR changes, which can possibly confound results. The difficulty of reliably interpreting endogenous ligand vs. receptors is commonplace in PET imaging as radioligand binding can only occur in available receptors. Further understanding can take place by depletion studies (e.g., AMPT for dopamine tracers), a technique not currently available for the KOR/dynorphin system. Another limitation is the use of the BSMSS as a measure of social status as several occupations listed are obsolete (e.g., typist) or not reflective of current professions (e.g., webmaster or software engineer, etc.). Nevertheless, along with others, we have shown important relationships previously with this measure [31, 32]. In females, the menstrual cycle was not controlled for, and while evidence has been shown that this has little to no effect on dynorphins in macaques [74], it could also be considered a limitation in the current work. Finally, age and BMI range are somewhat limited and therefore not conclusive.

Implications of this work can be far reaching if this is confirmed as a mechanism of socioeconomic stresses not only because of the central importance in understanding the physiological effects of society, but also because of the implications in psychiatric and addictive disorders. In fact, KOR pharmacologic treatments are being investigated in several conditions including major depressive disorder, anxiety spectrum disorders, substance use disorders, and clinical elements of stress [75, 76]. The effective management of social stressors in these conditions have long plagued us clinically and the KOR system could be of high utility in this regard.

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ADDITIONAL INFORMATION

Supplementary Information accompanies this paper at (https://doi.org/10.1038/s41386-019-0379-7).

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