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ORIGINAL ARTICLE

Revision: Externalizing behavior in healthy young adults is associated with lower cortisol responses to acute stress and altered neural activation in the dorsal striatum

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Abstract

The externalizing spectrum is characterized by disinhibition, impulsivity, antisocial-aggressive behavior as well as substance (mis)use. Studies in forensic samples and mentally impaired children suggested that higher rates of externalization are linked to lower cortisol stress responses and altered affect-related neural activation. In this fMRI-study, we investigated whether externalizing behavior in healthy participants is likewise associated with altered cortisol responses and neural activity to stress. Following a quasi-experimental approach, we tested healthy participants ($N = 61$, 31 males) from the higher versus lower range of the non-clinical variation in externalization (31 participants with high externalization) as assessed by the subscales disinhibition and meanness of the Triarchic-Psychopathy-Measure. All participants were exposed to Scan*STRESS*, a standardized psychosocial stress paradigm for scanner environments. In both groups, Scan*STRESS* induced a significant rise in cortisol levels with the high externalization group showing significantly lower cortisol responses to stress than the low externalization group. This was mainly driven by males. Further, individual increases in cortisol predicted neural response differences between externalization groups, indicating more activation in the dorsal striatum in low externalization. This was primarily driven by females. In contrast, *post-hoc* analysis showed that hypothalamic-pituitary-adrenal axis hyporeactivity in males was associated with prefrontal and hippocampal activation. Our data substantiate that individuals from the general population high on externalization, show reduced cortisol stress responses. Furthermore, dorsal striatum activity as part of the mesolimbic system, known to be sensitive to environmental adversity, seems to play a role in externalization-specific cortisol stress responses. Beyond that, a modulating influence of gender was disclosed.

KEYWORDS
cortisol, dorsal striatum, externalizing spectrum, fMRI, Scan*STRESS*

1 | INTRODUCTION

The externalizing spectrum encompasses a range of heterogeneous personality traits and behavioral patterns, primarily characterized by disinhibition, impulsivity, antisocial-aggressive behavior as well as substance (mis) use (Krueger et al., 2002, 2007; Patrick et al., 2013). It is closely related to, but conceptually distinct from psychopathy (Patrick, 2010), which is conceptualized by externalization and the additional phenotypic component boldness, expressing an underlying fearless disposition. For externalizing disorders (e.g., antisocial personality disorder, conduct disorder [CD] and substance (mis)use), it is assumed that there might exist common underlying etiological mechanisms. This idea is supported by behavioral genetics studies showing significant heritability of a general externalizing factor (Beauchaine et al., 2017; Blonigen et al., 2005; Hicks et al., 2007). In addition, in large samples derived from healthy as well as clinical populations, it could be shown that externalization is a dimensionally distributed characteristic that can be found also in the non-pathological range of variation (Krueger et al., 2007; Markon & Krueger, 2005). Such individuals show disinhibitory traits like increased aggression as well as impulsivity or elevated scores in disagreeableness and unconscientiousness within the five-factor model of personality. Furthermore, negative emotionality, low fearfulness, and low effortful control has been considered as most relevant pathways from individual temperament to externalizing psychopathology (Krieger & Stringaris, 2016).

From a developmental perspective, externalizing problems are related to deficits in emotion regulation as well as frequent stress exposure over the lifespan (Herts et al., 2012). The ability to react adequately to and cope with everyday emotion and stressful events has been considered one of the most relevant factors promoting mental health (Gross & Munoz, 1995). Thus, it can be hypothesized that externalization is linked to alterations in the psychobiological stress response not only in externalizing disorders, but also within its non-clinical variation.

Regarding externalization-specific hypothalamic-pituitary-adrenal (HPA) axis stress responses, the majority of studies so far has shown an inverse relationship between externalization and acute cortisol stress responses. These studies are based on clinical samples, for example, children and adolescents with conduct disorder and disruptive behavior disorder (Fairchild et al., 2008; Van Goozen et al., 2000), violent adult offenders (Virkkunen, 1985), and substance misusers (Couture et al., 2008). Interestingly, reduced HPA axis responses to acute stress in patients with high externalization seem to coincide with higher emotional reactivity (McLaughlin et al., 2011). However, other previous studies could not confirm HPA axis hyporesponsivity in externalization (Alink et al., 2008). It can be speculated that, at least in part, such results might be explained by the fact that some stress induction paradigms failed to reliably induce robust cortisol responses. When it comes to externalization in a non-clinical range, we are aware of only one study in healthy college students, which reports a negative association between cortisol responses to the trier social stress test (TSST) and psychopathy scores (O'Leary et al., 2007). Taken together, there is still a lack of data on psychobiological stress responses in healthy adults exhibiting externalizing behaviors within a subclinical range.

Besides the cortisol response to stress, other endocrine parameters appear to be linked to the externalizing spectrum as well. In particular, testosterone levels were shown to be higher in clinical samples with conduct disorder (Pajer et al., 2006) and antisocial behavior (Yildirim & Derksen, 2012). Thus, it could be hypothesized that testosterone concentrations are also elevated in non-clinical participants showing higher externalization in the non-clinical range.

Based on lesion and other animal studies, it is assumed that HPA axis (dys)regulation in humans is mediated by an influence of higher order brain and limbic areas (e.g., medial prefrontal cortices, amygdala, hippocampus). While activity of the hippocampus and anterior cingulate cortex (ACC) seem to reduce glucocorticoid reactivity, amygdala activity potentiates cortisol stress responses (for review see Herman et al., 2005). The fact that these regions also play a key role in psychosocial stress regulation in humans could be confirmed during the last years with brain imaging studies (Akdeniz et al., 2014; Dahm et al., 2017; Henze et al., 2020; Lederbogen et al., 2011). However, both the specific pattern of activation and deactivation and the direction of cortisol-related associations appear to depend strongly on the used paradigm (for review see Noack et al., 2019). In sum, to the best of our knowledge, so far, no study focused on neural stress regulation in relation to externalization in the non-clinical range.

Based on a large body of literature, there is a common neural dysfunctioning across externalizing disorders, in

particular hyporeactivity in the mesolimbic and the mesocortical systems. Following this, the externalizing spectrum seems to be linked to dysfunctional inhibitory control of limbic and mesolimbic regions by prefrontal areas. This is also proposed by the ontogenic process model of externalizing psychopathology by Beauchaine et al. (2016). Within this concept, HPA axis activity plays an important role in developing externalizing disorders. It is assumed that the facilitating effect of the amygdala and its connections to frontal regions including prefrontal cortex and orbitofrontal cortex (OFC) (e.g., processing of emotional cues) on HPA axis activity are impaired in externalizing disorders resulting in blunted cortisol responses to stress (see also Nikolas, 2016). Previous fMRI-studies already demonstrated that youth with conduct disorder (for review, see Fairchild et al., 2019), patients with substance (mis)use (Koob & Volkow, 2010) as well as with antisocial behavioral tendencies (Oberlin et al., 2012) showed reduced activity in response to rewarding stimuli and acute threat in OFC, ACC, striatum, and amygdala. One study provided support for the hypothesis that these alterations can partly be found within a healthy population exhibiting externalizing behavior. Foell et al. (2016) revealed that high externalization predicted reduced activation of the nucleus accumbens (ventral striatum) during a preparation phase and altered amygdala reactivity during viewing of pleasant and aversive pictures.

The objective of the present study was fourfold. First, we aimed at examining psychobiological stress responses in healthy men and women with high versus low externalizing behavior in the non-clinical range. We expected a lower cortisol response as well as higher emotional reactivity to acute stress exposure in participants with high externalization. Second, testosterone levels were hypothesized to be generally higher in participants with high externalization. Third, we assumed that participants exhibiting high compared to low externalizing behavior show reduced neural responses to Scan*STRESS*, especially in the amygdala, striatum (nucleus accumbens, nucleus caudatus and putamen), as well as prefrontal cortex (orbitofrontal and ACC). This expectation is based on the above-referenced blunted neural responses in these regions in externalizing disorders as well as their partly ascertained involvement in HPA axis regulation. Fourth, we aimed to identify brain regions associated with the assumed reduced cortisol stress response in participants with high compared to low externalization.

2 | Method

2.1 | Participants

Sixty-five participants (32 males, 33 females) were initially recruited in this quasi-experimental fMRI study. Prior to experimental sessions, eligibility of volunteers was ascertained with an online assessment, including questionnaires on demographic variables (e.g., age & gender), health status, MR-scanner contraindications, the Triarchic-Psychopathy-Measure (TriPM, Patrick, 2010; Patrick et al., 2009) and screening questions for the diagnostic modules of the Structured Clinical Interview for DSM-IV (SCID-II, Wittchen et al., 1997). Participants were selected from a pool of volunteers ($N = 784$) based on their scores in the two subscales disinhibition and meanness of the TriPM and they were assigned to a group with either high ($n = 33$) or low ($n = 32$) externalization. Participant selection was based on data gained in a validation study for the TriPM in the general population ($N = 1{,}476$) (Eisenbarth et al., 2012). For the present study, selected participants scored within the scopes of the highest ($Q_{0.75}$) or lowest quartile ($Q_{0.25}$) of the subscales disinhibition ($Q_{0.75} = 36$, $Q_{0.25} = 29$) and meanness ($Q_{0.75} = 33$, $Q_{0.25} = 26$) as derived from the aforementioned report. To avoid inclusion of individuals scoring high on psychopathy, volunteers scoring within the upper quartile of the TriPM subscale boldness ($Q_{0.75} = 55$) were not eligible for the present study. Further exclusion criteria were acute and chronic illness, mental and psychiatric disorders as assessed with the German version of the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I) and Axis II Personality Disorders (SCID-II, Wittchen et al., 1997), criminal history, current use of drugs and medication containing glucocorticoids as well as MR-scanner incompatibility. Two participants dropped out during the screening due to exclusion criteria. Females not using contraceptives ($n = 15$) were scheduled for the MRI sessions during the luteal phase of the menstrual cycle (Wolfram et al., 2011) determined by a chromatographic urinary ovulation test kit (gabmed GmbH, Köln, Germany).

Two further participants had to be excluded from the analysis after participation due to technical problems during the test session ($n = 1$) or poor image acquisition ($n = 1$). Thus, the final sample consisted of 61 participants (mean age 23.62 years, $SD = 3.81$, range: 18–34) comprising 31 males (16 with high externalization) and 30 females (15 with high externalization). Heart rate (HR) data were only available for $n = 54$ ($n = 12$ males, $n = 13$ with low externalization) because of insufficient data acquisition. One participant missed to fill in the Positive and Negative Affect Schedule (PANAS, Watson et al., 1988) questionnaire at the last time point (see section 3).

Prior to participation, all participants gave written informed consent. Afterward, they received a monetary compensation of 100 € or course credits. This experiment was approved by the ethics committee of the University of Regensburg.

2.2 | Procedure

For the scanner session, participants arrived 90 min prior to the test session inside the MRI scanner. During the initial 45 min relaxation phase, participants were watching a neutral movie. Fourty-five minutes prior to the start of the Scan*STRESS* paradigm (not before 1:00 p.m.), participants were administered 75 g customary glucose mixed with 200 ml of camomile tea to facilitate cortisol reactivity (Henze et al., 2020; Zänkert et al., 2020). The following one-hour MRI session consisted of the Scan*STRESS* paradigm (see Section 2.3), an 18 min resting state and a 12 min anatomy sequence. Subsequently, participants filled out a questionnaire package including the German version of the Barratt Impulsiveness Scale—Short Version (BIS-15, Spinella, 2007) and the "Wortschatztest" (WST, Schmidt & Metzler, 1994; see Section 2.5).

During the experimental session, we collected saliva samples by Cortisol Salivettes (Sarstedt, Nümbrecht, Germany) at ten time points: −75, −15, −1 min before the start of Scan*STRESS* as well as +15, +30, +50, +65, +80, +95 and +110 min (C1–C10) thereafter (see Figure 1). At each time point, participants completed the state version of the PANAS (Watson et al., 1988). For later testosterone analysis, native saliva was collected by passive drool using polypropylene tubes at three time points: −15 min before Scan*STRESS* onset and +65 min as well as +95 min thereafter (pooled for analysis). During Scan*STRESS*, we assessed HR in beats per minute (bpm) (see Figure 1).

On a second test day, participants performed a monetary Taylor Aggression Paradigm (mTAP), a second resting state and diffusion tensor imaging (DTI) sequence and completed another questionnaire package (results to be reported elsewhere).

2.3 | Scan*STRESS*

Scan*STRESS* is an adaption of the TSST for scanner environments consisting of two runs. According to Streit et al. (2014), participants were instructed to respond to a mental arithmetic and spatial mental rotation task (see Supplementary Figure S1) under a stress condition (performance trials, confrontation with an observation panel giving feedback) and a control condition (no observation and feedback by panel). We modified the initial protocol by prolonging the relaxing phase, administering the glucose drink and shortening the transition time into the scanner (see Henze et al., 2020). For detailed information, we refer to Supplementary Material 1.

2.4 | Materials, biochemical analysis, and data acquisition

After test sessions, saliva samples were stored at −20°C. Analyses were performed by the biochemical laboratory at the University of Trier, Germany. Cortisol was assayed in duplicate using a time-resolved immunoassay with fluorometric detection (DELFIA); testosterone was assessed by a commercially available assay kit (Demeditec Diagnostics GmbH, Kiel, Germany). Inter- and intra-assay coefficients of variation were below 10%, respectively. Visual inspection of individual cortisol trajectories and testosterone concentrations did not reveal any unphysiological levels.

HR was extracted for four second intervals with the MR compatible pulse oximeter Nonin Model 7500FO (Nonin Medical B.V., Minnesota, United States).

Participants were scanned in a MAGNETOM 3T Prisma scanner (Siemens AG; Erlangen, Germany) equipped with a 64-channel head coil. A T2*-weighted echo-planar imaging (EPI) sequence (TR = 2000 ms; TE = 30 ms, flip angle

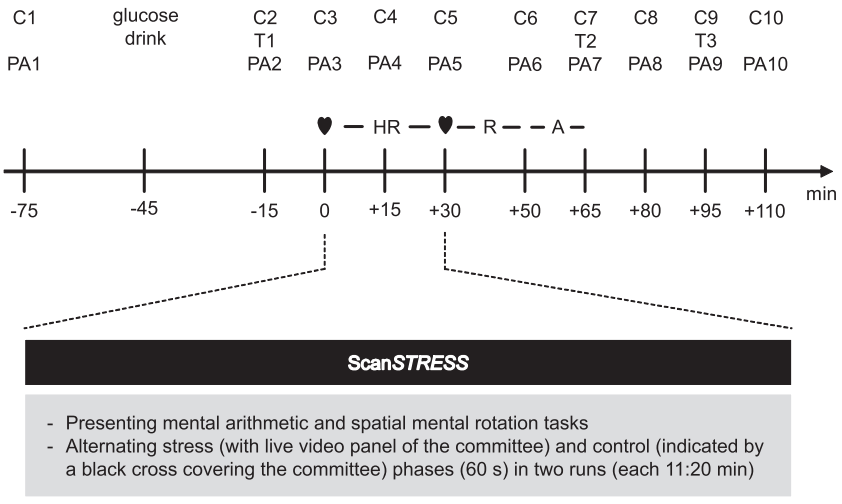

FIGURE 1 Flow chart of the experimental procedure during the MRI session including the Scan*STRESS* exposure. A, anatomy; C1–C10, cortisol samples; HR, heart rate; PA, positive and negative affect schedule; R, resting state; T1–T3, testosterone samples

= 90°, FOV = 192 × 192 mm², matrix size = 64 × 64 mm², 37 slices, slice thickness = 3.0, 1.0 mm gap, voxel size = 3 × 3 × 3 mm³, interleaved) was used resulting in 340 functional scans per run (in total 680) per participant and a T1-weighted magnetization-prepared rapid gradient-echo (MP-RAGE) sequence (TR = 2,400 ms, TE = 2.18 ms, flip angle = 9°, voxel size = 0.8 × 0.8 × 0.8 mm³, distance factor: 50%).

2.5 | Psychometric measures

We used the Triarchic-Psychopathy-Measure (TriPM, Patrick, 2010; Patrick et al., 2009) with 58 items comprising the three subscales disinhibition, meanness and boldness for the classification of our quasi-experimental groups (see above). Items of the TriPM are mainly adopted from the Externalizing Spectrum Inventory (Krueger et al., 2007). Items are answered on a 4-point scale ranging from 1 = *not true at all* to 4 = *completely true*. In a community sample a Cronbach's α of 0.87 for the total score proved as excellent (van Dongen et al., 2017). For the assessment of psychological responses to acute stress exposition, we applied the PANAS (Watson et al., 1988). The PANAS is a widely used 20 item-questionnaire assessing both positive and negative affect using a 5-point scale ranging from 1 = *not at all* to 5 = *very much*. Finally, the questionnaire package included the German version of the BIS-15 (Spinella, 2007) consisting of three subscales (nonplanning, motor impulsivity, attention impulsivity) and a total score as well as the WST (German for "vocabulary test", Schmidt & Metzler, 1994). The WST is a vocabulary test which was formerly introduced as a proxy for verbal intelligence.

2.6 | Data analysis

To assess potential differences between the two quasi-experimental groups in demographic variables, questionnaire scores and testosterone concentrations, we conducted Bonferroni-corrected independent Welch-test comparisons using R (version 3.5.1; R Core Team, 2018) with the packages afex (Singmann et al., 2020), car (Fox & Weisberg, 2019), haven (Wickham & Miller, 2019), psych (Revelle, 2019) and sjstats (Lüdecke, 2018). A power analysis resulted in a required total sample size of $N = 64$ subjects given a test power of 80% to detect at least moderate effect sizes ($d = 0.50$).

The parameter cortisol increase was defined by the difference between the individual cortisol peak (based on cortisol samples C5, C6, C7) and the pre-stress cortisol level (sample C3). Additionally, participants were grouped into responders versus non-responders according to the 1.5-nmol/l-criterion (Miller et al., 2013).

Further, using R, repeated measures analyses of variance (ANOVAs, Greenhouse–Geisser corrected) were performed for salivary cortisol ("time" [10 cortisol samples] × "gender" [female, male] × "externalization" [high, low]), HR ("condition" [stress, control] × "externalization" [high, low]) and affective stress response ("time" [10 assessments] × "externalization" [high, low]). For within-between interaction effects, a power analysis showed a required sample size of $N = 62$ subjects with a power of 80% to detect small effects with an effect size of $\eta_p^2 \geq 0.02$.

2.6.1 | fMRI data analysis

Imaging data were analyzed with FSL 6.0 (FMRIB's Software Library, www.fmrib.ox.ac.uk/fsl, Oxford, UK) using FEAT (FMRI Expert Analysis Tool). The following processing steps were conducted: motion correction by means of MCFLIRT, slice timing correction, non-brain removal using BET, intrasubject coregistration and registration to standard space defined by the Montreal Neurological Institute (MNI) using FLIRT and FNIRT, grand-mean intensity normalization, spatial smoothing with a Gaussian kernel of 8 mm full-width-at-half-maximum, high-pass filter correction of 120 Hz, time-series statistical analysis using FILM and region of interest (ROI) analysis applying fslmaths and featquery. The z (Gaussianized t/F) statistic images were thresholded nonparametrically using clusters determined by either $z > 3.1$ or $z > 2.3$.

For each run (first level analysis), a general linear model (GLM) was fitted with the two regressors of interest, namely stress and control, as well as eight regressors of no interest, namely the two announcement phases and the six realignment parameters. In a next step, data from each participant and run were entered into between-session analysis (second level) estimating mean responses for each participant. Subsequently, subject's mean responses were analyzed with a between-subject group model (third level) resulting in group mean responses (see Henze et al., 2020).

For condition- and group-specific effects on whole brain level, the statistical images were thresholded (two-tailed combined test) with family-wise error rate (FWE) $p < .025$ (two-tailed combined test, FWE < 0.05). The SPM Anatomy toolbox (Eickhoff et al., 2005) was appropriated for anatomy labeling. For condition-specific effects we performed one-sample paired t tests and for externalization effects two-sample t tests. *Post-hoc*, Bonferroni-corrected ROI analyses (repeated measures ANCOVAs, between-subject factor "externalization" [high, low]) were conducted using six predefined masks in amygdalae (520

voxels), ACC (1531 voxels), nucleus accumbens (126 voxels), putamen (1517 voxels), nucleus caudatus (901 voxels), and OFC (568 voxels; all bilaterally) as guided by the empirically derived hypothesis mentioned above (see introductory section). These binarized masks were created with the Harvard-Oxford cortical atlas, using fslmaths. During this binarization process, all voxels get the value one which have at least a probability of 50% for being part of the specific ROI; the other voxels contain the value 0. Subsequently, we extracted mean beta-values for each ROI.

Finally, a two-group model with continuous covariate using the grand mean centered cortisol increase was conducted to test whether the relationship between cortisol increase and the neural response differs between the high versus low externalization groups (high > low and low > high, thresholded at FWE < 0.05). For *post-hoc* ROI analyses (Bonferroni-corrected), the parameter estimates in significant brain locations (two masks) were entered into a multiple regression analysis with the categorical variable externalization and cortisol increase as continuous predictor. To capture potential gender effects, whole brain analyses were conducted separately for males and females (whole sample, FWE corrected at 0.05).

3 | RESULTS

3.1 | Descriptives

The comparison between the two quasi-experimental groups (high vs. low externalization) in demographic (age), behavioral (BIS-15, WST) and psychometric variables showed that participants solely differed significantly regarding the two expected dimensions of the TriPM, disinhibition (Cronbach's α: 0.88) and meanness (Cronbach's α: 0.91) as well as the four subscales of the BIS-15 (see Table 1).

3.2 | Endocrine, physiological, and psychological stress responses

Since we explicitly expected blunted cortisol responses to acute stress exposure in the high externalization group, we included responders as well as non-responders in the analyses. For salivary cortisol responses, we found a significant main effect of "time" (F[3.11,178.54] = 9.06, $p < .001$, $\eta_p^2 = 0.13$) as well as a significant interaction "time" by "externalization" (F(3.11,178.54) = 4.21, $p = .006$, $\eta_p^2 =$

TABLE 1 Mean ± *SD* of demographic, psychometric, behavioral, and hormonal data and results of welch tests comparing subjects with high versus low externalization groups

	High externalization		Low externalization					
	Male ($n = 16$)	Female ($n = 15$)	Male ($n = 15$)	Female ($n = 15$)	*t*	*df*	*p*-value	*d*
Age (yrs.)	24.31 (± 3.38)	21.87 (± 4.31)	25.67 (± 4.34)	22.53 (± 2.20)	0.98	58.94	.330	0.25
TriPM								
Disinhibition	40.25 (± 4.57)	43.07 (± 6.03)	27.07 (± 1.62)	27.20 (± 1.82)	−14.16	35.99	.001*	−3.60
Meanness	40.31 (± 5.45)	39.27 (± 3.85)	23.20 (± 1.86)	22.80 (± 1.86)	−18.52	39.25	.001*	−4.69
Boldness	47.75 (± 5.52)	47.60 (± 4.55)	51.53 (± 2.97)	48.67 (± 3.75)	2.17	54.85	.034	0.56
BIS-15								
Non-planning impulsivity	13.31 (± 3.11)	12.93 (± 3.37)	10.53 (± 2.67)	9.80 (± 2.40)	−4.03	56.75	.001*	−1.03
Motor impulsivity	11.56 (± 2.16)	11.87 (± 3.04)	10.13 (± 2.03)	9.73 (± 1.87)	−3.05	55.46	.001*	−0.78
Attentional impulsivity	11.38 (± 2.06)	11.33 (± 1.40)	9.8 (± 1.97)	9.40 (± 1.45)	−3.97	58.98	.004*	−1.02
Sum	36.25 (± 5.36)	36.13 (± 5.71)	30.47 (± 4.81)	28.93 (± 3.56)	−5.22	56.42	.001*	−1.33
WST raw	33.00 (± 2.10)	32.40 (± 1.64)	33.33 (± 4.24)	32.53 (± 2.00)	0.33	45.94	.746	0.08
Cortisol increase (nmol/L)	2.36 (± 2.09)	1.43 (± 2.85)	6.28 (± 6.46)	1.80 (± 1.65)	2.04	41.46	.047	0.53
Responder/ non-responder	10/6	6/9	11/4	4/11				

*Comparison survived Bonferroni correction at $p < .05$.

Abbreviations: BIS-15, Barratt Impulsiveness Scale – short version; TriPM, Triarchic-Psychopathy-Measure; WST, "Wortschatztest"; yrs., years; nmol/l, nanomol per liter.

0.07) with the high externalization group showing lower cortisol responses to stress ("time" [10 cortisol samples] × "externalization" [high, low]). The main effect of "externalization" did not reach significance ($F[1,59] = 2.74$, $p = .100$, $\eta_p^2 = 0.04$). Due to enhanced *SEM* in cortisol trajectories (see Figure 2), we performed cook distance analyses for cortisol increase and externalization in order to identify potential effects of variational cases. Analyses revealed no value over the cut-off of 1 while the more conservative 4/*N*-criterion was exceeded by three participants (3 males with low externalization) pointing to a possible moderate predominance of these cases. However, when excluding the three participants from cortisol analyses, the interaction "time" by "externalization" remained significant ($F[2.98,166.64] = 2.97$, $p = .034$, $\eta_p^2 = 0.05$).

Further covariance analyses revealed a significant effect of "gender" ($F[1,57] = 6.95$, $p = .011$, $\eta_p^2 = 0.11$) and a "time" by "gender interaction" ($F[3.22,177.39] = 3.32$, $p = .020$, $\eta_p^2 = 0.06$), indicating higher cortisol responses to stress in males (see Figure 2). The three-way interaction "time" by "externalization" by "gender" missed the level of significance ($F[3.22,177.39] = 2.34$, $p = .072$, $\eta_p^2 = 0.04$).

Exploratory, *post-hoc*-ANOVAs conducted separately for males and females yielded a "time" effect in both males ($F[2.88,83.46] = 7.37$, $p < .001$, $\eta_p^2 = 0.20$) and females ($F[3.14,87.84] = 3.56$, $p = .020$, $\eta_p^2 = 0.11$). The interaction "time" by "externalization" reached significance for males ($F[2.88,83.46] = 4.20$, $p < .001$, $\eta_p^2 = 0.13$; $F[2.29,59.49] = 2.43$, $p = .089$ if the three variational cases are excluded) but not for females ($F[3.14,87.84] = 0.76$, $p = .522$, $\eta_p^2 = 0.03$; see Figure 2a,b). Table 1 displays the number of responders and non-responders in the experimental groups. A chi-square test of independence with the variables group and (non)responder (see Table 1), testing whether the "externalization" effect could be causally associated with an unequal number of cortisol responders ($n = 31$) and non-responders ($n = 30$) in the two externalization groups, rendered non-significant ($\chi^2[df = 1] = 0$, $p = 1$).

Welch-test comparisons regarding testosterone concentrations did not show any significant differences between externalization groups ($t[58.79] = -0.55$, $p = .584$, $d = -0.14$; see Figure 2d).

Results from HR analysis yielded a significant main effect of "condition" ($F[1,52] = 86.75$, $p < .001$, $\eta_p^2 = 0.63$), but no significant difference between the two externalization groups ($F[1,52] = 0.08$, $p = .779$, $\eta_p^2 = 0.00$; see Figure 2c) and no interaction.

Analysis of affective stress responses showed a "time" effect for positive ($F[4.91,284.79] = 30.17$, $p < .001$, $\eta_p^2 = 0.34$) as well as negative affect ($F[3.64,214.69] = 29.89$, $p < .001$, $\eta_p^2 = 0.34$). Moreover, a main effect of "externalization" could be found for positive affect ($F[1,58] = 5.52$, $p = .020$, $\eta_p^2 = 0.09$) showing a significantly more positive affective state in the low externalization group. No other effects were significant. Affective stress responses are illustrated in Figure 2e,f.

3.3 | Manipulation check: Neural stress response

Contrasting stress versus control blocks (stress > control) on whole brain level, we observed a differential activation network including the left and right insula, the triangularis part of the left inferior frontal gyrus, left and right thalamus as well as left periaqueductal gray (see Supplementary Table S1). The opposite contrast (control > stress) was related to four clusters including the left and right prefrontal cortex (superior frontal gyrus, orbital gyrus), left posterior cingulate cortex, left and right insula as well as left and right basal forebrain (see Supplementary Table S2).

3.4 | Neural correlates of externalization

On whole brain level, no suprathreshold cluster could be observed by contrasting the high versus low externalization groups (high > low, low > high). None of the *post-hoc* ROI analyses revealed a significant externalization effect in the expected regions amygdala, ACC, nucleus accumbens, putamen, nucleus caudatus, and OFC bilaterally (Fs < 1.06, ps > .308). Further, analyses showed no significant externalization by gender interactions (Fs < 1.27, ps > .265).

To account for the association between CNS and HPA axis responsivity to acute psychosocial stress, the individual cortisol increase (grand mean centered) was used as a covariate (FWE-corrected $p < .05$). The linear relationship between the cortisol increase (see Table 1) and three clusters including the left putamen and left nucleus caudatus (dorsal striatum) was found to be different between the two groups showing more activation in the low externalization group (low > high, see Figure 3a and Supplementary Table S3). For the opposite contrast (high > low) no suprathreshold cluster survived. *Post-hoc* ROI analysis revealed a significant interaction effect "externalization" by "cortisol increase" using two masks in the bilateral putamen ($F[1,57] = 6.83$, $p = .011$, $\eta_p^2 = 0.11$) and nucleus caudatus ($F[1,57] = 5.62$, $p = .021$, $\eta_p^2 = 0.09$), surviving correction for the two significance tests. When excluding the above identified variational cases (see Section 3.2), this effect

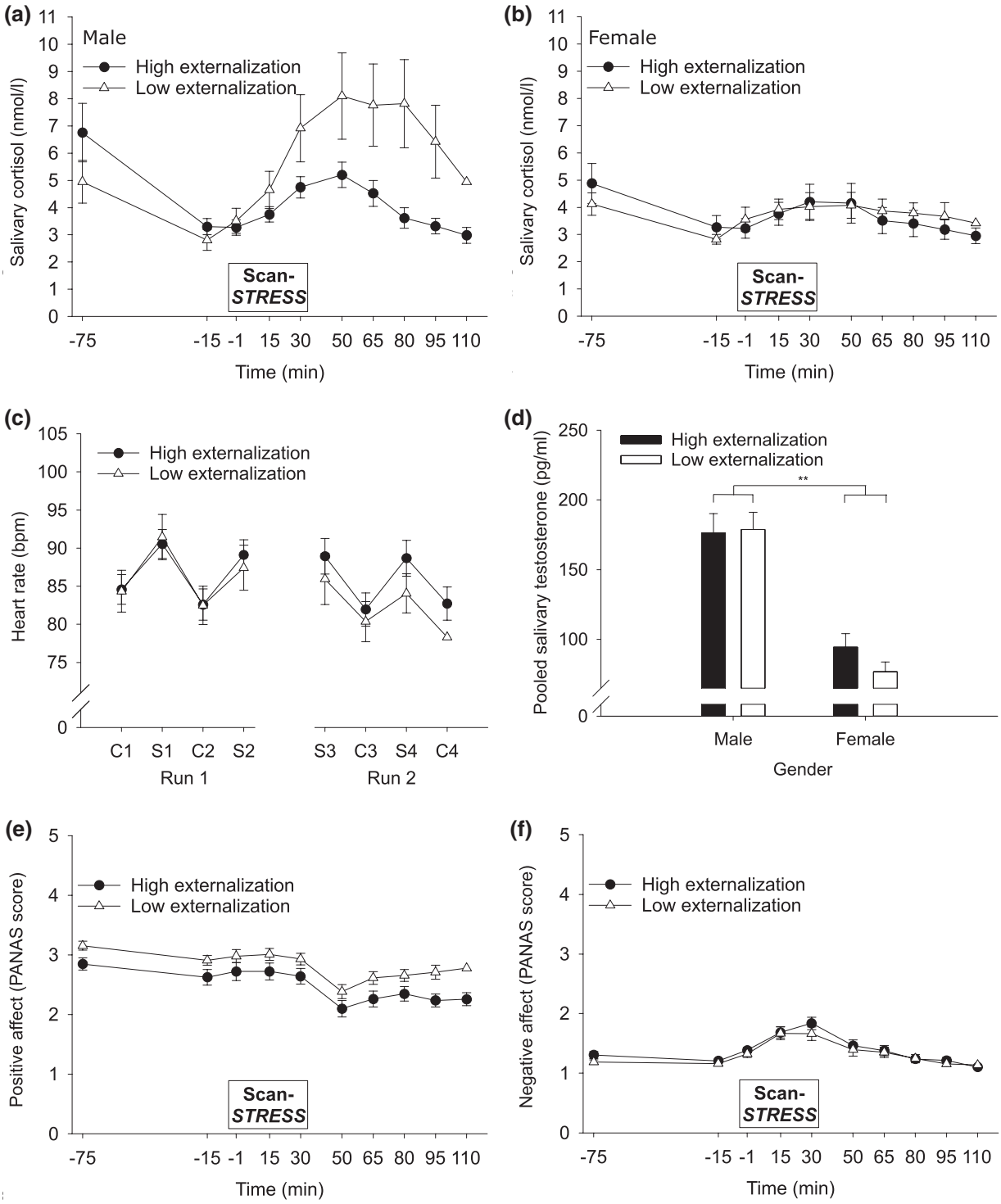

FIGURE 2 Hormonal, physiological and affective data comparing the high versus low externalization group. Salivary cortisol responses in (a) males and (b) females. Mean HR responses across conditions (C1–C4, control phases; S1–S4, stress phases) in run 1 and 2 (c). Pooled salivary testosterone concentrations in males and females (d). Positive and negative affect schedule scores for positive (e) and negative (f) affect. Error bars represent standard error of the mean. $^{**}p < .01$, $^{*}p < .05$

remains significant for the putamen ($F[1,54] = 4.18$, $p = .046$, $\eta_p^2 = 0.07$) and nucleus caudatus ($F[1,54] = 5.70$, $p = .021$, $\eta_p^2 = 0.10$), although the p-value for the putamen surpassed the Bonferroni corrected significance level. In order to test whether these effects might be mainly driven by high externalization, correlation analysis were

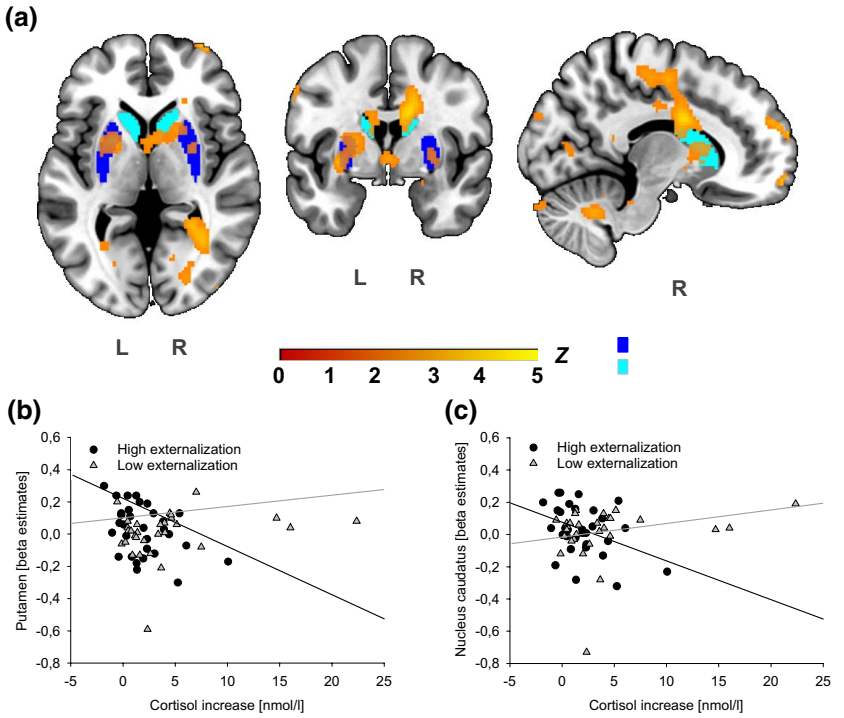

FIGURE 3 Externalization-group difference analysis (low vs. high externalization) with cortisol increase (continuous covariate) interaction (grand mean centered, two-tailed combined family-wise error-corrected $p < .05$) (a). Results of region of interest analyses for "externalization" by "cortisol increase" interaction using two masks in the bilateral putamen (b) and nucleus caudatus (C). L, left; R, right

performed. Indeed, a significant negative correlation between beta estimates and cortisol increases in the high externalization group ($n = 31$) could be observed in the putamen ($r = -0.41$, $p = .016$, one-tailed) and nucleus caudatus ($r = -0.39$, $p = .012$, one-tailed) surviving Bonferroni-correction. In contrast, in the low externalization group ($n = 30$), this correlation was non-significant (putamen: $r = 0.20$, $p = .140$, one-tailed; nucleus caudatus: $r = 0.23$, $p = .113$, one-tailed). Further, for both the putamen ($z = 2.66$, $p = .008$) and nucleus caudatus ($z = 2.37$, $p = .018$) correlation coefficients of the two externalization groups differed significantly from each other. Thus, in participants with high externalization, higher beta estimates during stress (vs. control) in the nucleus caudatus and putamen were associated with lower cortisol increases. In contrast, in participants with low externalization, beta estimates in these regions were not significantly linked to cortisol increases. Figure 3 depicts scatterplots of mean beta estimates and cortisol increases differentiated by externalization group in the bilateral putamen (Figure 3b) and nucleus caudatus (Figure 3c).

Finally, to explore gender differences in the covariation of externalization-specific neural stress responses and cortisol increases, the same whole brain procedure was applied for males and females separately. For females, results revealed one supra-threshold cluster (FWE corrected at 0.05) including the right putamen ($Z = 3.88$, $x = 20$, $y = 16$, $z = -2$) and left nucleus caudatus ($Z = 3.64$, $x = -12$, $y = 6$, $z = 18$). For males, we observed two supra-threshold clusters including the left hippocampus ($Z = 3.54$, $x = -26$, $y = -26$, $z = -8$), left pre- ($Z = 3.22$, $x = -38$, $y = 2$, $z = 38$) and postcentral ($Z = 3.44$, $x = -42$, $y = -8$, $z = 34$) gyrus as well as the left dorsolateral ($Z = 3.03$, $x = -52$, $y = 24$, $z = 38$) and ventrolateral ($Z = 3.31$, $x = -58$, $y = 28$, $z = 20$) prefrontal cortex.

4 | DISCUSSION

Over the last decades, evidence has accumulated that externalization in the pathological range is associated with altered psychobiological stress regulation. Based on these findings, the aim of the present study was to investigate cortisol and neural stress responses in relation to externalization in the non-clinical range.

We observed reduced cortisol responses to stress in healthy participants with high compared to low externalizing behavior reflected by the interaction "time" by "externalization". This finding is consistent with previous clinical findings (Fairchild et al., 2008; Van Goozen et al., 2000). Based on these studies, it was hypothesized that altered HPA axis responsivity in participants with high externalization may be associated with the experience of chronic stress. According to the concept of allostasis and allostatic load (McEwen, 1998), it was suggested that significant stress exposure during childhood and adolescence triggers recurring cortisol surges to acute stress and, if chronic, this might lead to a downregulation of HPA axis functioning in the long run (Alink et al., 2008). Other proposed concepts explaining the link between externalizing behavior and hyporeactivity are sensation-seeking

(Robinson & Berridge, 1993) and low-fear (Raine, 2013) theories. They suggest that individuals with a physiological under-arousal might engage in sensation-seeking behaviors in order to stimulate themselves by, e.g., antisocial behavior. Therefore, it is assumed that blunted cortisol responses are associated with reduced experiences of fear, which would be required for learning from negative consequences of one's actions (e.g., by punishment). Thus, such individuals should engage more frequently in externalizing behavior. Here, we showed for the first time that externalization is associated with altered HPA axis responsivity not only in the pathological but also in the sub-clinical range. Although highly speculative, HPA axis dysregulation could, at least, serve as a potential sensitive marker or even operate as risk factor for the development of externalizing problems on a clinically relevant level.

In the present study, males and females differed significantly in their salivary cortisol response to acute stress with males showing larger cortisol responses, a generally well-documented effect (Zänkert et al., 2019). It is assumed that gender differences are, for example, attributable to sexual dimorphisms in brain functioning (e.g., corticolimbic system), circulating gonadal steroids (e.g., estradiol, testosterone) and/or gender-specific interpretations of stressors (Kudielka & Kirschbaum, 2005). Based on this, it is not surprising that we also found a moderating influence of gender on externalization-specific HPA axis responses. A comparable results pattern was found in the study by O'Leary et al. (2007) examining gender differences in the association between stress-related cortisol responses and psychopathic personality traits in the general population. While women showed non-significant cortisol increases regardless of psychopathy, men with low psychopathic traits responded significantly higher to the TSST compared to men with high psychopathy. Potential candidates for explaining these gender differences in externalization-specific HPA axis reactivity might be differences in brain functioning or the influence of androgens, especially testosterone, at different levels of the HPA axis (O'Leary et al., 2007). Beyond such biological reasoning, it might also be possible that the much lower cortisol responses to stress in our female subsample made it much more unlikely to detect potential group differences in cortisol responses related to externalization in women than men. Thus, considering the observed gender effects in the present study and given the paucity of data on women with externalizing behavior, we recommend to focus more on female samples in future investigations.

It was speculated earlier that testosterone acts as a potential biomarker regarding the externalizing spectrum (Pajer et al., 2006; Yildirim & Derksen, 2012). However, against our hypothesis, our current data revealed no difference in salivary testosterone concentrations between high and low externalizing participants, beyond the expected gender difference in testosterone levels. This is in line with a recent meta-analysis that reported only limited evidence for testosterone effects (Dekkers et al., 2019). The absence of such an effect could be due to the fact that we studied healthy participants showing externalizing behaviors within the non-clinical range. Thus, it might be speculated that differences in testosterone levels manifest only with larger deviations or only in the pathological range.

In respect to autonomic functioning, we did not observe any differences in stress-induced HR responses related to externalization. This appears to be in contrast to earlier studies that reported lower cardiovascular stress responses in clinical samples within the externalizing spectrum (McBurnett et al., 2005; Snoek et al., 2004). However, empirical evidence so far is rather inconsistent (Van Goozen et al., 1998).

At the affective experience level, exposure to Scan*STRESS* increased negative affect and declined positive affect. The current data shows that healthy participants with high externalizing behaviors showed a constantly lower positive affective state while the negative affect was comparable to participants with low externalization. This could be alluding to the hypothesis that participants with externalizing behavior in the subclinical range might be in particular characterized by a generally lowered positive affect while overreaching affective responses to acute stress might be (only) symptomatic for pathological externalizing behavior.

Beside the question regarding satisfactory test power with the given sample size, one further explanation for the absence of an effect of externalization in whole brain level analysis contrasting stress and control might be our non-clinical sample. This assumption is supported by studies investigating group differences in healthy nonclinical participants scoring high versus low on psychopathy (Buckholtz et al., 2010; Gordon et al., 2004). The majority of these studies also reported no group differences on whole brain level whereas ROI analyses revealed at least strong associations between psychopathy scores and activity in amygdala, prefrontal cortex, and functional connectivity in the striatum. In the current experiment, ROI analyses in the expected regions of interest, however, likewise disclosed no significant difference between externalizing groups in neural activity.

To identify brain regions associated with the observed reduced HPA axis responses to acute psychosocial stress in high externalizing participants, we additionally entered the variable cortisol increase to the statistical models. Results indicate that the relationship between cortisol increase and neural activity including the putamen and nucleus caudatus (dorsal striatum) differed between externalization groups. *Post-hoc* ROI analyses revealed that

this relationship was negative in participants with high externalization, as verified by significant negative correlations between beta estimates and cortisol increases. In contrast, respective correlations remained nonsignificant in participants with low externalization. This points to the idea that the effects are mainly driven by high externalization. It appears relevant that externalization (in particular trait impulsivity), also within the non-clinical range, was previously found to be associated with a hypo-responsive mesolimbic dopamine system (e.g., nucleus accumbens, ventral regions of the nucleus caudatus, putamen) as well as an inappropriate modulation of mesolimbic pathways by prefrontal areas (Beauchaine et al., 2017). Indeed, earlier studies provided some evidence that the mesolimbic dopamine system is sensitive to environmental adversity during development (Gatzke-Kopp, 2011), which might explain alterations in its functioning related to high externalization. Moreover, a positive correlation between cortisol stress responses and dopamine release in the mesolimbic pathway, especially the nucleus accumbens, could be observed (Oswald et al., 2005; Pruessner et al., 2004). Following from here, it could be assumed that the observed lower HPA axis response in the high externalization group is associated with a cortisol-related reduced dorsal striatum activation as part of the reactive mesolimbic system.

Exploratory, *post-hoc* analyses further revealed that the "externalization" by "cortisol increase" effect in the dorsal striatum could mainly be found in females. In males, activation in the hippocampus as well as dorsolateral and ventrolateral PFC was stronger related to cortisol increases in the low compared to high externalization group. This is partly supported by studies suggesting a gender-specific neural activation network underlying the central stress response with enhanced responses in the striato-limbic system in females and stronger activation in prefrontal areas in males (Dedovic et al., 2009; Wang et al., 2007). Although recent findings suggest no clear functional distinction for particular neural structures but rather dissociating associations for males and females (Henze et al., 2021). As shown recently, the stress response in the dorsal striatum seems to be greater in females than males (Goldfarb et al., 2019) while evidence regarding the direction is rather inconsistent (Kogler et al., 2015). While the hippocampus is known to be involved in regulating HPA axis functioning (Pruessner et al., 2008), it is, of course, not specifically related to stress responses in males. At least, there exist earlier findings showing that externalization is related to stress-related alterations in the hippocampus. For example, smaller hippocampi volume were observed after early life stress in children exhibiting behavior problems (e.g., disruptive behavior; Hanson et al., 2015; Teicher et al., 2012). It is further known that functional changes in the hippocampus are linked to chronic stress and allostatic load (for review see McEwen, 2001). Taken together, the male-specific HPA axis hyporeactivity in the high externalization group in the present study is related to prefrontal and hippocampal activation. Indeed, the hippocampus is known to exert a negative feedback function on HPA axis regulation (Pruessner et al., 2008). This points to the idea that externalization, particularly in males, might thus come along with reduced HPA axis stress responsivity. This is interesting because males normally show higher HPA axis stress responses than females (Zänkert et al., 2019). Otherwise, in the first place, the reduced cortisol-related striatum responsivity in high externalizing females combined with the non-significant "externalization" effect in female cortisol responses appear to be a complex pattern. Potentially, we could not detect a significant externalization effect in females due to their generally lower cortisol responses. However, at least on a descriptive level, a difference in cortisol increases could be observed between externalization groups in females (see Table 1), predicting cortisol-related activation in the dorsal striatum known to be involved in female stress regulation.

Based on these different lines of research, one might raise the question whether a phenotypic characteristic on the behavioral level, namely high versus low externalization, could be linked to the observed differences in HPA axis and mesolimbic functioning. In this context, studies should be acknowledged that suggest a reallocation of neural network activity toward the salience network in response to acute stress, resulting in enhanced automatic and habitual responses mediated by the dorsal striatum (Vogel et al., 2015). It is assumed that this shift is coordinated, among others, by cortisol (Schwabe et al., 2013). The difference in the neural network shift between high and low externalizing participants consisting of an altered cortisol-related neural activity in the dorsal striatum could result in a maladaptive recruitment of resources in high externalizing participants. Such resources might be essential for an appropriate response to acute stress and (un) availability could reflect individual deviations on the behavioral and emotional level (e.g., impulsivity, emotional reactivity). Taken together, this might indicate an insufficient neural network shift to salience reflecting a state of under-arousal as proposed by sensation-seeking and low-fear theories.

Several limitations should be taken in account for the current study. First, we only included university students resulting in a limited generalizability of our results. Second, we inquired gender by simply asking about self-reported gender identity. Thus, biological sex was not assessed, but may also impact on psychobiological stress responses. Third, we can also not preclude a potential impact of any physical or psychological inconvenience

experienced by participants inside the scanner on our data. However, we attempted to catch such possible unsystematic effects by the within block design of the Scan*STRESS* paradigm. Fourth, due to our strict inclusion criteria (e.g., high vs. low externalization, MR-compatibility, health status) other potentially confounding variables like use of contraceptives could not be kept constant leading to a partly heterogeneous sample. Fifth, indeed, we reached a reasonable large sample size for detecting statistically relevant effects. However, a recently conducted analytic approach showed a strong influence of sample size on result stability and interpretation in univariate fMRI analysis recommending increasing sample sizes for studies investigating brain-behavior correlations (Grady et al., 2021).

5 | CONCLUSIONS

In sum, the applied Scan*STRESS* paradigm reliably induced acute stress responses in terms of cortisol, HR and affective responses. As a main finding, we observed that high externalization, though still in the non-clinical range, came along with reduced acute cortisol stress responses as well as a generally lower positive affective state. This finding might provide further evidence for the assumption that externalization is a dimensionally distributed characteristic ranging from variations within the non-clinical range to more extreme extents of externalization (e.g., antisocial personality disorder, conduct disorder, and substance (mis)use). During psychosocial stress exposure, no differences in neural activity between participants with high versus low externalization could be observed. However, in the high externalization group, cortisol increases correlated negatively with dorsal striatum activity. This observation raises the idea that differences in the neural network shift mediated by the dorsal striatum might be associated with externalizing behavior via stress-related HPA axis regulation. Additionally, a modulating influence of gender was disclosed in HPA axis regulation. In males, HPA hyporeactivity was associated with prefrontal and hippocampal activation. In contrast, on the neural level results indicated reduced cortisol-related dorsal striatum activity notable in high externalizing females, which did not lead to a significant "externalization" effect in cortisol responses to stress.

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SUPPORTING INFORMATION

Additional Supporting Information may be found online in the Supporting Information section.

FIGURE S1 Example of a mental arithmetic and spatial mental rotation task during stress and control condition

TABLE S1 Activation peaks within a significant cluster contrasting stress versus control (two-tailed combined test, family-wise error corrected at 0.05)

TABLE S2 Activation peaks within a significant cluster contrasting control versus stress (two-tailed combined test, family-wise error corrected at 0.05)

TABLE S3 Activation peaks within a significant cluster (stress vs. control) covarying with cortisol increase contrasting subjects exhibiting low versus high externalization (family-wise error $p < .05$)

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