

# Reduced Real-life Affective Well-being and Amygdala Habituation in Unmedicated Community Individuals at Risk for Depression and Anxiety

Oksana Berhe, Anna Höflich, Carolin Moessnang, Markus Reichert, Thomas Kremer, Gabriela Gan, Ren Ma, Urs Braun, Ulrich Reininghaus, Ulrich Ebner-Priemer, Andreas Meyer-Lindenberg, and Heike Tost

**BACKGROUND:** Early identification of risk for depression and anxiety disorders is important for prevention, but real-life affective well-being and its biological underpinnings in the population remain understudied. Here, we combined methods from epidemiology, psychology, ecological momentary assessment, and functional magnetic resonance imaging to study real-life and neural affective functions in individuals with subclinical anxiety and depression from a population-based cohort of young adults.

**METHODS:** We examined psychological measures, real-life affective valence, functional magnetic resonance imaging amygdala habituation to negative affective stimuli, and the relevance of neural readouts for daily-life affective function in 132 non-help-seeking community individuals. We compared psychological and ecological momentary assessment measures of 61 unmedicated individuals at clinical risk for depression and anxiety (operationalized as subthreshold depression and anxiety symptoms or a former mood or anxiety disorder) with those of 48 nonrisk individuals and 23 persons with a mood or anxiety disorder. We studied risk-associated functional magnetic resonance imaging signals in subsamples with balanced sociodemographic and image quality parameters (26 nonrisk, 26 at-risk persons).

**RESULTS:** Compared with nonrisk persons, at-risk individuals showed significantly decreased real-life affective valence ( $p = .038$ ), reduced amygdala habituation (familywise error-corrected  $p = .024$ , region of interest corrected), and an intermediate psychological risk profile. Amygdala habituation predicted real-life affective valence in control subjects but not in participants at risk (familywise error-corrected  $p = .005$ , region of interest corrected).

**CONCLUSIONS:** Our data suggest real-life and neural markers for affective alterations in unmedicated community individuals at risk for depression and anxiety and highlight the significance of amygdala habituation measures for the momentary affective experience in real-world environments.

<https://doi.org/10.1016/j.bpsc.2022.06.009>

Early diagnosis, treatment, and ideally prevention of psychiatric disorders in the population is desirable, but the existing knowledge about daily-life psychological and neural affective alterations in community-based individuals at mental health risk is limited (1). Meta-analyses suggest that about 10% of all individuals in the general population experience subclinical symptoms of anxiety (2) and depression (3), and a significant proportion of these individuals will eventually transition to manifest psychiatric disorders (4,5). However, many persons fall below the binary threshold of current diagnostic systems, which defines the difference between mental health and disorder based on the presence of a predefined number and duration of psychiatric symptoms. Consequently, community-based individuals with daily-life subclinical symptoms often remain unnoticed and not sufficiently attended to, in both clinical and research settings (6).

From a community care and prevention standpoint, 2 groups of individuals are of particular relevance for the study of the underresearched “gray area” between mental health and disorder: those who currently experience subthreshold symptoms but do not have a history of psychiatric illness and those who have had a psychiatric disorder in the past but do not currently experience any obvious clinical signs (1). In this work, we define these groups as community-based individuals at mental health risk. We derive this view from studies and discourses in the field that have critically addressed the clinical validity of diagnostic boundaries between normal and pathological mood and anxiety experiences (7,8). Here, evidence suggests that there is a smooth transition between pathological depression and anxiety and milder emotional experiences (1) and that subthreshold prodromal and residual states carry a substantial risk of progression to more severe states over the

life course (9,10). In our definition of mental health risk in the community, we thus put forward (and later explore) the notion that both risk groups map to a shared (subclinical) continuum of clinically relevant phenomena in between mental health and disease. At the biological level, the grouping of the 2 at-risk groups is supported by studies showing comparable abnormalities of subthreshold prodromal and residual states in social reward processing (11,12), in cognitive domains such as cognitive control and executive function (13–16), and in resting-state functional connectivity (17,18). We further propose that the improved understanding of the daily-life psychological and neural characteristics of such risk states is important because the identification of salient risk markers can guide the development of novel early interventions at multiple, synergistic levels of influence, including in the areas of community mental health services, digital mental health, and neurofeedback therapy (19,20).

Important leads for this work came from the recent literature that emphasizes the unspecific nature of symptoms at subclinical stages of psychiatric illnesses (1,21,22). In addition, dimensional models of psychopathology such as the CHARMS (clinical high at risk mental state) study served as important conceptual influences, which promote the transdiagnostic investigation of subclinical risk markers and mechanisms to inform future preventive and predictive approaches (22–24). Indeed, the existing data suggest significant alterations in the daily-life experience in persons at clinical risk for mood and anxiety disorders (25–27). These include, among others, higher negative affect and lower hedonic capacity in real-world contexts, i.e., changes in daily experience that can be addressed with e-health based interventions. At the neural system level, altered habituation of the amygdala to threatening stimuli is a good candidate for mechanistic investigation. This view is supported by the demonstrated reliability of the phenotype (28) as well as its documented role as an evolutionarily conserved neural mechanism for affective processing and behavioral adaptation (29,30). Altered amygdala habituation has further been associated with a range of psychiatric disorders and related risk constellations (31–35), including in community-based samples and across a dimensional range of symptom severity for anxiety, depression, and stress-related disorders (36–39). However, studies in community-based individuals at clinical risk are still scarce and the interpretation of existing data is often complicated by concomitant, interfering factors such as the preferential inclusion of help-seeking individuals or the contamination of neural readouts by confounding factors (e.g., treatment effects). Also, barely any studies on this topic to date have seized the opportunity of contemporary multimodal ecological neuroscience approaches, which allow for the coordinated inquiry of clinical, neural, and daily-life psychological functions in naturalistic cohorts (25).

In this study, we combined methods from epidemiology, clinical psychology, ecological momentary assessment (EMA), and functional magnetic resonance imaging (fMRI) to study affective functions in community-based persons at clinical risk for depression and anxiety disorders derived from a population-based cohort of young, non-help-seeking adults. We used EMA with smartphone-based e-diaries to study momentary affective responses in real-world environments (40), fMRI, and a well-established implicit emotion processing

task (41) to uncover alterations in amygdala signaling, and probed the significance of the identified neural phenotype for the affective experience in daily life.

We studied EMA and questionnaire data in 61 unmedicated individuals at clinical risk, 48 demographically similar nonrisk persons and 23 community-based individuals identified as fulfilling the criteria for a current mood or anxiety disorder. We derived all study participants from the same naturalistic population by random selection. We hypothesized that momentary affective valence in daily life would be significantly lower in the at-risk and clinical groups than in the nonrisk group. We further compared fMRI readouts between carefully matched subsamples of 26 unmedicated persons at clinical risk and 26 nonrisk individuals to identify alterations in neural affective signaling related to community psychiatric risk in the absence of demographic, medication, and image quality confounds. Here, we expected to see a blunted amygdala habituation in community-based persons at clinical risk reminiscent of that of clinical states (31,32,34). We further expected these neural affective signals to be relevant for the real-life affective experience of the nonrisk individuals, persons at clinical risk, or both groups. Beyond formal hypothesis testing, we further explored other EMA and questionnaire measures to yield novel insights into the nature and range of altered affective functions in community-based individuals at clinical risk.

## METHODS AND MATERIALS

### Study Participants and Clinical Assessment

The Psychoepidemiological Center at the Central Institute of Mental Health in Mannheim, Germany, recruited a total of 349 individuals for this study. Participants were young adults in the age range 18 to 28 years, which we randomly drew from local population registries based on a 2-stage proportionally layered procedure [see (40,42) for details]. General exclusion criteria were the presence of a relevant medical or neurologic disorder. We assessed past and current psychiatric symptoms through screening forms and Mini-DIPS (Short Interview for Mental Disorder) interviews (43–45) that were evaluated by 2 independent clinical raters (AH and TK). The Mini-DIPS covers the most common mental disorders in adulthood according to ICD-10 and clarifies the presence of psychopathologically relevant experiences for the diagnostic categories. Based on these assessments, we defined 4 initial participant groups: 1) individuals with current psychiatric symptoms above the diagnostic threshold (clinical group,  $n = 23$ , mean age:  $23.17 \pm 2.68$  years, 20 females), 2) individuals with 1 or more current symptoms on the mood-anxiety spectrum that did not qualify for the diagnosis of a psychiatric disorder (subclinical group,  $n = 40$ , mean age:  $22.37 \pm 2.55$  years, 33 females), 3) clinically remitted individuals with a personal history of relevant psychiatric symptoms in the past who denied current presence of psychopathologically relevant experiences (history group,  $n = 21$ , mean age:  $22.82 \pm 3.01$  years, 12 females), and 4) healthy nonrisk individuals who were free of any current or former psychiatric symptoms, diagnosis, or treatment (healthy nonrisk group,  $n = 48$ ,  $21.86 \pm 1.56$  years, 39 females) that we derived from a larger sample of nonrisk individuals.

We later combined the individuals of the subclinical and history groups to a joint group of community-based individuals

## EMA and fMRI Signals in Community Individuals at Risk

at mental health risk because we expected that both groups would map on a shared continuum of affective alterations in between mental health and disease (24) (see [Results](#), [Table S1](#), and [Figure S1](#)). None of the at-risk individuals had received psychotropic medication in the preceding 12 months of study and only 1 of the persons was currently in formal psychiatric care ([Table S2](#) and [Figure S2](#)). We then drew a sample of 48 individuals from the total pool of 264 identified nonrisk individuals using internal software to achieve a nonrisk group with a comparable distribution of basic sociodemographic characteristics (i.e., age, sex, education) with the combined at-risk group.

After study inclusion, we first collected questionnaire measures on time-stable psychological constructs. Subsequently, we collected EMA data over 7 days in everyday life. We performed the neuroimaging examination of the study participants immediately after the end of the EMA study week (i.e.,  $1.50 \pm 1.36$  [minimum./maximum = 0/6] days after EMA completion). We compared the acquired questionnaire and e-diary measures between the groups to identify psychological and real-life indicators of community mental health risk ([Table 1](#)). For the ensuing neuroimaging analysis of risk indicators, we compared subgroups of 26 at-risk and 26 nonrisk individuals with available neuroimaging data that we carefully matched for a broader panel of sociodemographic attributes and data quality indicators known for impacting mental health-related neural readouts (e.g., fMRI task performance, fMRI image quality metrics [including temporal signal to noise ratio, spikes, translation/rotation metrics, and framewise displacement], socioeconomic status, current urbanicity, adverse childhood experiences) (see [Table S3](#)) (19).

The fMRI at-risk group included 18 individuals from the subclinical group and 8 individuals from the history group. All enrolled study participants provided written informed consent for a protocol approved by the Medical Ethics Committee II of the Medical Faculty Mannheim at the Ruprecht-Karls-University in Heidelberg, Germany.

### Psychological Data Acquisition and Analysis

We acquired a battery of well-established psychological and demographic questionnaires quantifying socioeconomic status (46), perceived social status (47,48), degree of current urbanicity (49), trait anxiety (50), loneliness (51), self-efficacy (52), sense of coherence (53), optimism (54), perceived mental well-being (55), satisfaction with life (56), perceived daily hassles (57), chronic stress (58), coping strategies (59,60), perceived social support (61), and retrospective self-ratings of adverse childhood experiences (62). We provide further details on the assessed questionnaires in [Table S4](#). We assessed group differences in SPSS (version 25; IBM Corp.) using variable type and distribution appropriate tests (i.e.,  $\chi^2$  test, classical analysis of variance [ANOVA], Welch's ANOVA, Kruskal-Wallis H test) (see [Table 1](#) for details).

### e-Diary Data Acquisition and Analysis

We assessed e-diary-ratings for 7 consecutive days in daily life with study smartphones (Motorola Moto G, Motorola Mobility) and a flexible time and location-based sampling scheme with 9 to 23 prompts per day in between 7:30 AM and 22:30 PM (minimum/maximum interval: 40/100 minutes) as previously

detailed (40,42,63). Our primary interest was to capture potential alterations in real-life affective valence in clinically at-risk individuals. For this, we used a well-known short scale for EMA with established psychometric properties (64) capturing within-subject fluctuations in real-life affective valence with the 2 bipolar items "content" to "discontent" (German Translation: zufrieden–unzufrieden) and "unwell" to "well" (German translation: unwohl–wohl) presented at the edges of 2 computerized visual analog scales with sliding locators (score range of 0–100). We instructed participants to place, upon each e-diary prompt, the locators at the scale positions representing their momentary affective state. We averaged the 2-item scores to use as dependent variables in our multilevel analyses.

For exploratory analyses, we further calculated an established EMA measure of daily-life affective (in)stability [i.e., the mean square of successive differences in valence (65)] and assessed e-diary items quantifying momentary calmness and energetic arousal, social contact (63), social anhedonia (63), and the appraisal of negative and positive events (66,67). e-Diaries and sampling strategy were implemented using the ambulatory assessment software movisensXS (version 0.6.3658; movisens GmbH). We used multilevel models in SAS (version 9.4; SAS Institute Inc.) to test for group differences, thereby nesting within-subject e-diary assessments (level 1) within participants (level 2) and using a categorical group variable (level 2) (68). We provide further details on the EMA acquisition and analysis methods in the [Supplement](#). All participant groups surpassed an average compliance rate of 70% and we covaried for between-group differences in compliance in our multilevel analysis ([Table S5](#)).

### fMRI Data Acquisition and Preprocessing

We performed blood oxygen level-dependent fMRI on a 3T MRI scanner (Siemens Trio) using a well-established implicit emotion processing paradigm with 2 task conditions (emotional face matching, shapes matching) (41), providing reliable measures of amygdala habituation (28). We processed and analyzed the fMRI data using SPM12 (<http://www.fil.ion.ucl.ac.uk/spm>) implemented in MATLAB (version R2013b; The MathWorks, Inc.). Data preprocessing consisted of standard procedures. We provide further methods details on the used fMRI sequence, paradigm, and preprocessing routines in the [Supplement](#).

### Amygdala Activation and Habituation Analysis

fMRI data analysis consisted of a 2-level procedure. At the first level, we defined a general linear model for each subject that included the boxcar reference vectors for the task blocks of the 2 conditions (convolved with the standard SPM hemodynamic response function) and the 6 head motion parameters from the realignment step (covariates of noninterest). During model estimation, we defined a high-pass filter with a cutoff frequency of 262 seconds to remove low frequency signal components and used first-order autoregressive modeling to correct for temporal autocorrelations. We computed individual maps of voxelwise habituation indices as previously described (28) by calculating the mean response amplitude difference between the first and the last block of the face matching

**Table 1. Sample Description for Community Subject Groups**

Characteristics	Nonrisk Group, <i>n</i> = 48		Clinical At-Risk Group, <i>n</i> = 61		Clinical Group, <i>n</i> = 23		ANOVA/ $\chi^2$ /H Test/MLA <sup>a</sup>		Nonrisk vs. Risk	Risk vs. Clinical	Nonrisk vs. Clinical
	Mean $\pm$ SD/Count (Range) or <i>n</i>	<i>n</i>	Mean $\pm$ SD/Count (Range) or <i>n</i>	<i>n</i>	Mean $\pm$ SD/Count (Range) or <i>n</i>	<i>n</i>	$\beta$ Value	<i>p</i> Value	<i>p</i> Value <sup>b</sup>	<i>p</i> Value <sup>b</sup>	<i>p</i> Value <sup>b</sup>
<b>Demographic Data</b>											
Age, Years	21.86 $\pm$ 1.56 (18.14–25.58)	48	22.53 $\pm$ 2.7 (18.10–27.83)	61	23.17 $\pm$ 2.68 (18.88–27.30)	23	2.63	.076	–	–	–
Sex, Female/Male	39/9	48	45/16	61	20/3	23	2.01	.366	–	–	–
Education, Years	12.48 $\pm$ 1.29 (10–16)	48	12.68 $\pm$ 1.78 (8–16)	60	12.61 $\pm$ 1.67 (10–16)	23	0.21	.784	–	–	–
SES	12.80 $\pm$ 3.00 (6.20–19.40)	48	13.47 $\pm$ 3.31 (6.90–20.20)	61	11.20 $\pm$ 2.88 (5.50–15.30)	23	4.40 <sup>c</sup>	.014 <sup>c</sup>	.512	.009 <sup>c</sup>	.088
<b>Psychological Data</b>											
Trait Anxiety, STAI-T, Sum	33.00 $\pm$ 6.78 (20–50)	47	39.82 $\pm$ 9.60 (21–66)	60	52.09 $\pm$ 10.71 (34–71)	23	35.52 <sup>c</sup>	<.001 <sup>c</sup>	<.001 <sup>c</sup>	<.001 <sup>c</sup>	<.001 <sup>c</sup>
Mental Well-being, WHO-5, Sum	16.52 $\pm$ 4.15 (10–25)	48	15.19 $\pm$ 4.57 (4–23)	59	11.05 $\pm$ 5.77 (2–23)	20	9.91 <sup>c</sup>	<.001 <sup>c</sup>	.259	.019 <sup>c</sup>	.002 <sup>c</sup>
Satisfaction With Life, SWLS	27.74 $\pm$ 4.35 (14–35)	47	25.77 $\pm$ 6.09 (9–34)	60	21.00 $\pm$ 8.72 (5–32)	23	9.95 <sup>c</sup>	<.001 <sup>c</sup>	.128	.057	.04 <sup>c</sup>
BCOPE-Adaptive Coping	42.72 $\pm$ 5.10 (31–52)	47	41.33 $\pm$ 7.74 (21–56)	60	40.52 $\pm$ 7.46 (27–54)	23	2.16	.336	–	–	–
BCOPE-Maladaptive Coping	21.26 $\pm$ 3.93 (15–32)	47	23.68 $\pm$ 4.45 (15–36)	59	25.26 $\pm$ 4.28 (18–36)	23	7.28 <sup>c</sup>	.001 <sup>c</sup>	.012 <sup>c</sup>	.393	.001 <sup>c</sup>
Self-Efficacy, SWE, Sum	29.85 $\pm$ 4.24 (21–38)	48	29.05 $\pm$ 4.38 (17–40)	60	25.91 $\pm$ 5.47 (19–35)	23	6.04 <sup>c</sup>	.003 <sup>c</sup>	.60	.049 <sup>c</sup>	.012 <sup>c</sup>
Loneliness, UCLA, Mean	29.37 $\pm$ 6.94 (20–48)	48	34.32 $\pm$ 11.22 (20–76)	60	39.91 $\pm$ 16.74 (20–87)	23	7.27 <sup>c</sup>	.002 <sup>c</sup>	.016 <sup>c</sup>	.314	.020 <sup>c</sup>
Optimism, LOT-R, Optimism Sum	16.98 $\pm$ 3.47 (9–23)	48	15.60 $\pm$ 4.48 (4–23)	60	12.04 $\pm$ 5.44 (0–22)	23	10.14 <sup>c</sup>	<.001 <sup>c</sup>	.174	.023 <sup>c</sup>	.001 <sup>c</sup>
Perceived Social Support, BSSS, Sum	31.17 $\pm$ 1.63 (25–32)	48	29.85 $\pm$ 3.16 (19–32)	60	27.69 $\pm$ 5.76 (15–32)	23	8.36 <sup>c</sup>	<.001 <sup>c</sup>	.135	.030 <sup>c</sup>	.001 <sup>c</sup>
SOC, Sum	152.79 $\pm$ 17.73 (115–189)	48	138.76 $\pm$ 20.90 (88–181)	59	114.95 $\pm$ 23.17 (64–152)	22	26.65 <sup>c</sup>	<.001 <sup>c</sup>	.001 <sup>c</sup>	<.001 <sup>c</sup>	<.001 <sup>c</sup>
Daily Stress, ABF	2.04 $\pm$ 0.63 (1.09–3.88)	42	2.50 $\pm$ 0.76 (1.09–4.75)	47	2.90 $\pm$ 1.02 (1.84–5.42)	15	8.36 <sup>c</sup>	<.001 <sup>c</sup>	.007 <sup>c</sup>	.360	.017 <sup>c</sup>
Early Adversity, CTS	5.96 $\pm$ 1.99 (5–16)	48	6.65 $\pm$ 2.08 (5–16)	60	8.45 $\pm$ 3.91 (5–17)	22	7.83 <sup>c</sup>	.001 <sup>c</sup>	.19	.119	.023 <sup>c</sup>
<b>EMA<sub>d</sub></b>											
Valence, MDBF <sup>e</sup>	75.82 $\pm$ 11.63 (48.99–99.14)	47	69.04 $\pm$ 10.18 (47.88–89.59)	61	60.10 $\pm$ 14.85 (28.19–84.32)	22	10.90 <sup>c</sup>	<.001 <sup>c</sup>	.038 <sup>c</sup>	.012 <sup>c</sup>	<.001 <sup>c</sup>
Energetic Arousal, MDBF <sup>e</sup>	60.76 $\pm$ 12.76 (27.96–85.49)	47	56.00 $\pm$ 11.35 (30.72–79.58)	61	49.89 $\pm$ 11.21 (30.31–70.68)	22	4.30 <sup>c</sup>	.016 <sup>c</sup>	.254	.277	.014 <sup>c</sup>
Calmness, MDBF <sup>e</sup>	72.16 $\pm$ 13.04 (36.60–98.59)	47	66.48 $\pm$ 11.02 (45.38–89.19)	61	57.43 $\pm$ 14.37 (27.39–86.71)	22	8.47 <sup>c</sup>	<.001 <sup>c</sup>	.164	.016 <sup>c</sup>	<.001 <sup>c</sup>
Alone, Alone/Not Alone <sup>f</sup>	34/72	47	31/6	61	31/61	22	0.40	.673	–	–	–
Rather Be Alone <sup>e</sup>	11.20 $\pm$ 9.59 (0.73–38.43)	47	16.32 $\pm$ 14.34 (1.57–65.14)	61	25.7 $\pm$ 20.34 (1.21–63.92)	22	8.28 <sup>c</sup>	.002 <sup>c</sup>	.315	.009 <sup>c</sup>	.001 <sup>c</sup>
Do Not Like the Company <sup>e</sup>	10.70 $\pm$ 12.99 (0.63–77.17)	47	14.14 $\pm$ 14.34 (0.70–65.80)	61	17.81 $\pm$ 14.09 (2.91–59.92)	22	4.18 <sup>c</sup>	.018 <sup>c</sup>	.39	.199	.014 <sup>c</sup>
Positive Event Appraisal <sup>e</sup>	23.14 $\pm$ 11.31 (2.54–48.68)	47	24.97 $\pm$ 14.29 (1.39–56.04)	61	23.35 $\pm$ 10.69 (2.36–44.84)	22	0.26	.771	–	–	–
Negative Event Appraisal <sup>e</sup>	8.91 $\pm$ 6.18 (0.67–33.22)	47	12.78 $\pm$ 7.36 (0.68–32.56)	61	17.16 $\pm$ 11.45 (6.32–56.63)	22	6.44 <sup>c</sup>	.002 <sup>c</sup>	.119	.110	.002 <sup>c</sup>
Affective (In)Stability, Valence MSSD	235.24 $\pm$ 166.31 (1.07–793.75)	47	337.06 $\pm$ 219.35 (16.75–897.15)	61	592.98 $\pm$ 479.70 (75.49–2141.76)	22	6.53 <sup>c</sup>	.002 <sup>c</sup>	.887	.002 <sup>c</sup>	.007 <sup>c</sup>

Table 1. Continued

Characteristics	Nonrisk Group, n = 48		Clinical At-Risk Group, n = 61		Clinical Group, n = 23		ANOVA/ $\chi^2$ /H Test/MLA <sup>a</sup>		Nonrisk vs. Risk vs. Clinical	
	Mean ± SD/Count (Range) or n	n	Mean ± SD/Count (Range) or n	n	Mean ± SD/Count (Range) or n	n	$\beta$ Value	p Value	p Value <sup>b</sup>	p Value <sup>b</sup>
e-Diary Prompts per Day	12.56 ± 1.32 (9–15)	47	12.29 ± 1.07 (10–15)	61	12.56 ± 1.29 (10–15)	22	0.744	.453	–	–
e-Diary Compliance (%) <sup>d</sup>	85.61 ± 11.49% (57.58%–100%)	47	77.81 ± 19.00% (32.93%–100%)	61	73.79 ± 19.59% (32.91%–100%)	22	4.271 <sup>c</sup>	.011 <sup>c</sup>	.054	1.000

Broad-based changes in the clinical group on most outcome measures compared with limited changes in the at-risk group in areas involving stress experience, negative emotions, and personal coping skills. For details on the psychological questionnaires including acronyms, see Table S4. n includes number of participants with available data. Univariate analysis of variance (ANOVA) was performed. Multilevel analysis (MLA) was performed while controlling for time of the day and time of the day-squared (level 1) and differences in compliance (level 2). ABF, AlltagsbelastungsFragebogen; BCOPE, brief coping orientation to problems experienced; BSSS, Berliner Social Support Skalen; CTS, childhood trauma screener; EMA, ecological momentary assessment; LOT-R, Life Orientation Test-Revised; MDDBF, Mehrdimensionale Befindlichkeitsfragebogen; MSSD, mean square of successive differences of valence ratings; SES, socioeconomic status; SOC, sense of coherence; STAI-T, State-Trait Anxiety Inventory-Trait; SWE, Selbstwirksamkeitserwartung; SWLS, Satisfaction With Life Scale; UCLA, University of California Los Angeles; WHO-5, World Health Organization-Five Well-Being Index.

<sup>a</sup>Statistical tests:  $\chi^2$  tests for group comparisons with categorical variables, ANOVA and Tukey tests for group comparisons and variables with equal variance and normal distribution, Welch-ANOVA and Games-Howell tests for group comparisons with normally distributed variables with unequal variance (as identified by Levene's test), Kruskal-Wallis and Dunn tests for group comparisons with not-normally distributed variables with (unequal variance).

<sup>b</sup>All p values of post hoc pairwise group comparisons are Bonferroni corrected for multiple group comparisons.

<sup>c</sup>p Values < .05.

<sup>d</sup>Aggregation of EMA indices within and between subjects for use for sample description only.

<sup>e</sup>Mean/day/participant.

<sup>f</sup>Number of prompts participants have been alone out of all prompts across 7 days of measurement.

<sup>g</sup>Percentage of answered prompts.

condition (block 1 > block 4). At the second level, we entered these maps into univariate ANOVA models with group (clinical at-risk, nonrisk) as factor. Consistent with our previous work (31), we defined a group contrast to test for the hypothesized amygdala habituation deficits in community-based individuals at clinical risk (clinical at-risk < nonrisk). We further tested for general and group-specific associations between daily-life affective valence and amygdala habituation estimates. For this, we used univariate ANOVA models with the mean individual EMA-derived valence measures and a corresponding interaction term (group × valence) as regressors of interest, respectively.

**fMRI Statistical Inference**

We assessed statistical significance at  $p < .05$ , peak voxel-level familywise error (FWE) corrected for multiple comparisons within an a priori defined anatomical region of interest mask of the right amygdala derived from the Wake Forest University PickAtlas (69). As in our previous work (31), we chose the right amygdala as an a priori region of interest for hypothesis testing because the literature suggests a different functional role and habituation rate for the right amygdala, with a specialization for the rapid and dynamic detection of affective stimuli (70–72) and a higher retest reliability of habituation estimates (28).

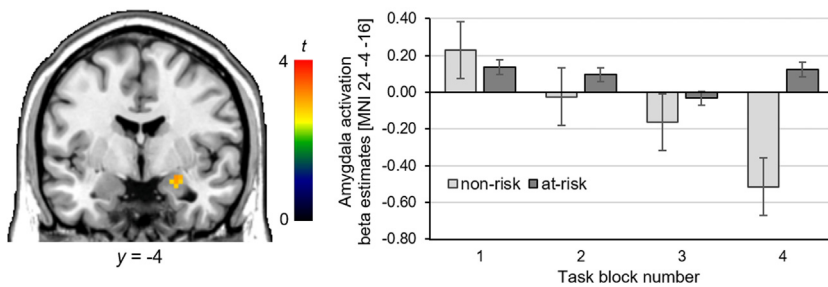
**RESULTS**

**Psychological Questionnaire Data**

Descriptive analysis of psychological data revealed a regular pattern across variables, with the group means of the at-risk group mapping in between those of the nonrisk group and the clinical group. Inferential statistics revealed significant differences in the at-risk group for daily hassles, maladaptive coping, and perceived loneliness compared with the nonrisk group (all  $ps < .016$ , all reported p values were Bonferroni corrected for multiple group comparisons) but not with the clinical group (all  $ps > .31$ ). In contrast, in other psychological variables such as perceived mental well-being, satisfaction with life, optimism, self-efficacy, and social support, at-risk persons did not differ significantly from the nonrisk group (all  $ps > .12$ ) but differed significantly from the clinical group (all  $ps < .05$ ). For trait anxiety and dispositional sense of coherence, at-risk individuals displayed fully intermediate properties, in that they differed significantly from both the nonrisk group and the clinical group (all  $ps < .001$ ). We provide further statistical details in Table 1. There were no significant group differences in psychological questionnaire data between the community-based subgroups at mental health risk (i.e., subclinical group vs. history group) (see Table S2 and Figure S2 for details).

**Daily-life EMAs**

Daily-life affective valence in the at-risk individuals was significantly lower than that of the nonrisk group ( $p = .038$ , all p values were Bonferroni corrected for multiple group comparisons) and significantly higher than that of the clinical group ( $p = .012$ ). Exploratory analyses suggested no group differences in the frequency of social contacts and the appraisal of positive



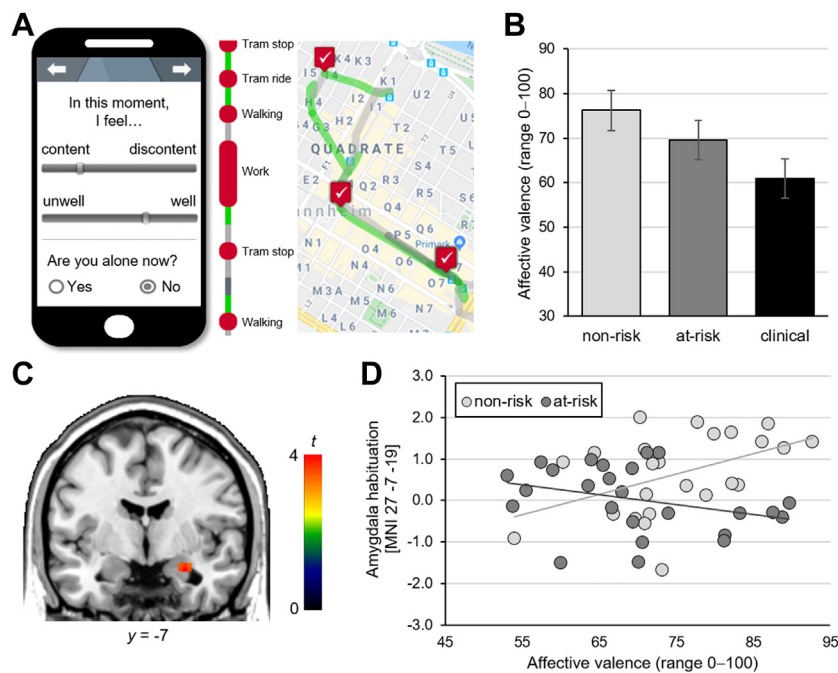
template magnetic resonance image. The plot shows habituation estimates (and standard errors of the mean) of the peak voxel in the right amygdala for each functional magnetic resonance imaging task block and group, respectively. MNI, Montreal Neurological Institute standard space.

events (all reported  $p$ s > .67). We further did not detect any group differences between the at-risk group and the nonrisk group for affective (in)stability, negative event appraisal, liking of social contact, preference of being alone, and momentary feelings of calmness and energetic arousal (all  $p$ s > .11). In contrast to this, individuals in the clinical group exhibited widespread changes in these variables, which distinguished this group from both at-risk and nonrisk groups. We provide further statistical details in Table 1 and Table S5.

### Amygdala Habituation Analyses

Comparison of the at-risk group and the nonrisk group confirmed a significant reduction of right amygdala habituation to repeated negative affective stimuli in the at-risk individuals ( $t_{1,50} = 3.03$ ,  $p_{FWE} = .024$ , all reported  $p$  values are peak-level corrected for region of interest) (Figure 1, left). This finding

also survived correction for a bilateral amygdala mask ( $t_{1,50} = 3.03$ ,  $p_{FWE} = .047$ ). In the nonrisk individuals, data inspection suggested a high initial responsivity of the right amygdala followed by a rapid decline in activity with successive emotional block repetitions, whereas in the at-risk individuals the amygdala responsivity appeared blunted and uniform over time (Figure 1, right). A regression analysis with daily-life affective valence scores as a predictor did not provide evidence for a significant association with amygdala habituation across all individuals ( $t_{1,49} = 1.96$ ,  $p_{FWE} = .330$ ). However, we detected a significant group by EMA valence interaction effect on right amygdala habituation ( $t_{1,48} = 3.70$ ,  $p_{FWE} = .005$ ; after correction for a bilateral amygdala mask:  $t_{1,48} = 3.70$ ,  $p_{FWE} = .009$ ) (Figure 2). Post hoc regression analysis confirmed that higher right amygdala habituation was significantly related to higher daily-life affective well-being in the nonrisk group ( $t_{1,24} = 3.33$ ,  $p_{FWE} = .012$ ; after correction



**Figure 2.** Study methods and amygdala habituation–affective valence associations. **(A)** Illustration of the smartphone-based assessment of affective valence in daily life in connection with a person's movement pattern in downtown Mannheim. Left: visualization of the affective valence and social contact e-diary items. Smartphone image by ElisaRiva (<http://www.pixabay.com>). Right: white check marks on a red background displayed on the route symbolize positions where e-diary assessments were prompted (for illustration purposes, not real study participant). **(B)** Significant group differences in ecological momentary assessment valence between community-based individuals not at clinical risk, those at clinical risk, and those with a current mood or anxiety disorder. Community-based individuals at clinical risk display significantly lower valence levels than nonrisk persons, and significantly higher valence levels than individuals in the clinical group; error bars display standard error from the multilevel analysis (for details see Table 1). **(C, D)** Differential association of amygdala habituation and affective valence in daily life in community persons at clinical risk compared with those not at risk ( $t = 3.70$ , familywise error corrected  $p = .005$ ). The functional map in panel **(C)** is thresholded at  $p = .005$ , uncorrected for illustration purposes, and is displayed on the coronal section of a structural-template magnetic resonance image. The scatterplot in panel **(D)** depicts the associations of the habituation estimates (extracted from the

amygdala peak voxel) and valence values for the 2 groups. The reported interaction analysis finding in imaging space also survived familywise error correction after excluding 1 outlier from the analysis. MNI, Montreal Neurological Institute standard space.

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for a bilateral amygdala mask:  $t_{1,24} = 3.33$ ,  $p_{FWE} = .024$ ) but not in the at-risk group ( $t_{1,24} = 0.96$ ,  $p_{FWE} = .76$ ).

## DISCUSSION

In this study, we took a multimodal ecological neuroscience approach to identify psychological, real-world, and neural markers of altered affective function in unmedicated individuals at clinical risk for mood and anxiety disorders drawn from a population-based cohort of young adults. Specifically, we aimed to characterize the psychological profile of at-risk individuals in the community, determine the nature and extent of their current affective alterations in daily life, and examine the relevance of the neural signals examined to real-world affective experience. We obtained several interesting results, which we discuss below.

In terms of psychological profile, we posited that community-based individuals at clinical risk are on a continuum of change that spans between healthy nonrisk individuals and individuals with a current manifest disorder. At the descriptive level, we observed just this: Mean scores for the risk group were intermediate between those of the other 2 groups in all variables and our supplemental analysis revealed no significant differences between the history and subclinical subgroups, which we combined into 1 risk group. At the same time, the areas in which at-risk persons differed significantly from the nonrisk individuals were relatively specific, while the group with a manifest disorder showed clear changes in almost all of the areas examined. Specifically, significant differences in at-risk individuals clustered around variables indicating heightened stress awareness, a tendency to negative emotions, and a limited ability to use personal resources to cope with such experiences. These focal differences presented against a background of mostly unremarkable functions and resources, such as preserved satisfaction with life, optimism, and social support. We conclude from these data that psychological alteration in the community is a gradual phenomenon and the psychological profile of individuals with subclinical mood and anxiety symptoms is comparable with that of fully remitted individuals with a previous mood or anxiety disorder. Furthermore, the clear salient psychological deficits of community-based individuals at clinical risk appear selective and involve the processing of stress and negative emotions.

Regarding the nature and extent of daily-life impairments, we hypothesized that young community-based individuals with subclinical depression and anxiety would show a significant reduction in affective valence, and our study results confirmed this assumption. Although there are few comparable studies to date, this finding aligns well with our own findings on the effect of psychiatric risk and resilience factors on real-life affective valence (40,63) and changes in emotional experience of children and adolescents with subclinical symptoms reported in other community-based EMA studies (73–75). In relative terms, our exploratory analysis of other EMA outcomes further suggests selective changes in the daily-life experience of community-based individuals at clinical risk. Precisely, while the clinical group differed significantly in almost all measures recorded, including those indicative of daily-life depressed mood, reduced drive, social anhedonia, affective instability, and increased stress experience, the decrease in affective

valence in the at-risk subjects seemed to occur against a background of otherwise unremarkable real-life functions. Together with the psychological profile elaborated above, this suggests that community-based individuals at increased risk for mood and anxiety disorders exhibit selective risk phenotypes on the behavioral and experiential level, including limited personal resources to cope with stress-associated experiences and a reduction in affective valence in daily life. In addition to traditional psychotherapy, deficits in the daily-life experience can be addressed with targeted ecological moment interventions, especially when the real-world risk marker or target phenomenon is known, as in this case (76).

At the neural systems level, our results identified reduced amygdala habituation in community-based individuals with subclinical depression and anxiety. Specifically, whereas the nonrisk group showed a decrease in estimated amygdala response of about 60%, it was only 1% for the risk subjects (emotional stimulation block 1–4). The amygdala plays an evolutionarily conserved role in threat processing (77), and the robust habituation phenotype studied (28) reflects a basic neural plasticity mechanism that supports a basic and innate form of learning. Specifically, it protects the organism from repeatedly responding to threat-associated stimuli with no meaningful consequences for survival, thereby freeing up important neural and behavioral resources for more pressing tasks. The detected difference in habituation in community-based individuals at risk is thus suggestive of a neural plasticity-related alteration in the affective processing of environmental stimuli in this group. In our nonrisk individuals, amygdala response habituated as expected and predicted increased momentary affective valence, indicating the relevance of this neurofunction in daily life. This link was not found in our community-based individuals at clinical risk, whose diminished real-life affective well-being was unrelated to amygdala habituation. Although further experiments will be necessary to determine the origin of this dissociation, we speculate that reduced biological plasticity in the amygdala may require alternative regulatory strategies to deal with perceived threat (e.g., cognitive appraisal), which may disrupt the direct link of amygdala habituation to real-life affective well-being. Deficient amygdala habituation as such is unlikely specific to certain psychiatric disorders (31,78) or sources of illness risk (31,79,80). However, because amygdala function can be directly targeted and modulated with neurofeedback-based interventions (81), this neural risk phenotype is an attractive candidate for novel multimodal treatment (and ideally prevention) concepts with multiple, synergistic starting points.

The results presented must be evaluated against the background of some limitations of our study, which we explain below. First, the size of the studied groups is limited. This is mainly because we obtained our participants from an epidemiological sample of young adults in the population, in which the prevalence of subclinical syndromes and full remissions of a previous disorder is finite. Second, we departed from a purely population-based approach by matching the composition of the nonrisk comparison group using a set of predefined demographic and treatment-related variables. We consider both of these decisions important because we wanted to reflect as closely as possible the situation of young, non-help-seeking, and clinically vulnerable individuals in the community, while

minimizing bias in our results from confounding variables that are known to affect the outcomes we studied. Third, we could not consistently apply the 3-group design of the questionnaire and EMA analyses in neuroimaging space because we did not have enough usable fMRI data from the clinical group. However, because our primary goal was to study a neuronal risk marker in individuals from the general population in the absence of treatment effects, the availability of sufficient patient data for this purpose would have been of limited help anyway. Fourth, beyond affective valence, the reported EMA results are based on exploratory analyses, and any interpretations based on these findings are therefore preliminary. However, we felt it was important to report these data and our opinions in this regard, as they may promote the formation of new hypotheses in future studies. Finally, the reported associations between neural and everyday affective measures are based on cross-sectional data and therefore do not allow for causal interpretations. We speculate that the relationship between brain function and everyday experience is a complex, reciprocal causal process, an assumption that should be further explored in future experimental studies.

## ACKNOWLEDGMENTS AND DISCLOSURES

This research was supported by grants from the German Research Foundation, Research Training Group GRK2350/1 (project B02 [to HT and AM-L]), Collaborative Research Center 1158 projects B04 (to HT) and B09 (to AM-L), and Collaborative Research Center TRR 265 projects A04 (to HT and UE-P) and S02 (to UE-P and AM-L). Additional support was received from the Ministry of Science, Research and Arts of the State of Baden-Wuerttemberg, Germany (Grant Nos. 42-5400/136/1 [to HT and AM-L] and 42-04HV.MED(16)/16/1 [to AM-L]), the German Federal Ministry of Education and Research (Grant No. 01EF1803A [to AM-L, HT and UE-P]), Heidelberg University (Olympia-Morata Program, [to GG]), German Academic Exchange Service (to GG), and Chinese Scholarship Council (to RM).

We thank Beate Höchemer, Kristina Schwarz, Ceren Akdeniz, Janina I Schweiger, Carina Sebald, Alexander Moldavski, and our research assistants for valuable support.

AM-L has received lecture fees from the Lundbeck International Foundation, Paul-Martini-Stiftung, Lilly Deutschland, Atheneum, fama Public Relations, IDIBAPS, Janssen-Cilag, Hertie-Stiftung, Bodelschwingh-Klinik, Pfizer, Universität Freiburg, Schizophrenia Academy, Hong Kong Society of Biological Psychiatry, Spanish Society of Psychiatry, Italian Society of Biological Psychiatry, Reunions I Ciencia S.L. Brain Center Rudolf Magnus UMC Utrecht, Friedrich-Merz-Stiftung, and consultant fees from Boehringer Ingelheim, Elsevier, Brainsway, Lundbeck Int. Neuroscience Foundation, Lundbeck A/S, Sumitomo Dainippon Pharma Co., Academic Medical Center of the University of Amsterdam, Synapsis Foundation-Alzheimer Research Switzerland, IBS Center for Synaptic Brain Dysfunction, Blueprint Partnership, University of Cambridge, Dt. Zentrum für Neurodegenerative Erkrankungen, Zürich University, Brain Mind Institute, L.E.K. Consulting, ICARE Schizophrenia, Science Advances, Fondation FondaMental, von Behring Röntgen Stiftung, The Wolfson Foundation, and Sage Therapeutics. UE-P reports consultancy for Boehringer Ingelheim. All other authors report no biomedical financial interests or potential conflicts of interest.

## ARTICLE INFORMATION

From the Department of Psychiatry and Psychotherapy (OB, AH, CM, MR, TK, GG, RM, UB, UE-P, AM-L, HT) and the Department of Public Mental Health (UR), Central Institute of Mental Health, Medical Faculty Mannheim, University of Heidelberg, Mannheim; Mental mHealth Lab (MR, UE-P), Department of Sport and Sport Science, Karlsruhe Institute of Technology, Karlsruhe; Department of eHealth and Sports Analytics (MR), Ruhr-University Bochum, Bochum, Germany; Department of Psychiatry and Psychotherapy (AH), Medical University of Vienna, Vienna, Austria; Centre

for Epidemiology and Public Health (UR), Health Service and Population Research Department, Institute of Psychiatry, Psychology and Neuroscience, London; and ESRC Centre for Society and Mental Health (UR), King's College London, London, United Kingdom.

OB, AH, AM-L, and HT contributed equally to this work.

Address correspondence to Heike Tost, M.D., Ph.D., at [heike.tost@zi-mannheim.de](mailto:heike.tost@zi-mannheim.de).

Received Jan 24, 2022; revised May 27, 2022; accepted Jun 15, 2022.

Supplementary material cited in this article is available online at <https://doi.org/10.1016/j.bpsc.2022.06.009>.

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