## **Supplementary material**

1. **Methods**

## **Ecological Momentary Assessment (EMA)**

For EMA data collection, the RealLife Exp application (associated to the Lifedatacorp platform) was installed on the smartphone of each participant. If a participant did not own a smartphone (*n* = 3), the application was installed on a tablet or a family member’s smartphone that was loaned to the participant during the duration of the study. We also ensured that the participant had good knowledge of the functioning of the tablet/smartphone. We used a semi-random signal-contingent sampling scheme with eight notifications per day (ranging between 7:30 AM and 10:00 PM) for six consecutive days, resulting in a maximum of 48 beeps per person. At each beep, participants were instructed to respond to a short questionnaire on the application on their mobile phone. A window of at least 30 minutes was scheduled between two consecutive notifications. Participants had 15 minutes to respond to a notification before it expired. During the installation, participants were briefed extensively about the EMA protocol and completed a test questionnaire with the examiner to make sure that they understood all the questions as well as the 7-point Likert scale or multiple-choice answers for giving their responses. During the EMA period, the participants’ compliance was monitored and they were contacted several times by a member of the research team to keep them motivated for the protocol. Questionnaires completed in more than 15 minutes were excluded. In addition, responses that were completed in less than one minute were examined individually, and those with a clear pattern of response (i.e., the same response to each item) were excluded because of potential careless responding. In line with previous studies (e.g., Myin-Germeys, van Os, Schwartz, Stone, & Delespaul, 2001), only participants who completed a full questionnaire for at least one-third of the beeps were included in the analyses.

## **EMA measures**

**Affects and momentary psychotic experiences**

Positive and negative affects as well as momentary psychotic experiences were assessed with several items, each measured on a scale from 1 (“not at all”) to 7 (“extremely”). Within-person centered data were entered in a factor analysis with oblimin rotation to examine factor structure of the items. The results revealed a 3-factor structure with eigenvalues greater than 1:

 **Positive affects (PA)** were assessed using the mean score of four items: *“I feel relaxed”, “I feel content/cheerful”, “I feel excited”, “I have confidence in myself”* (respective loadings were 0.52, 0.74, 0.78 and 0.52; Cronbach’s α = 0.6).

 **Negative affects (NA)** were assessed using the mean score of five items: *“I feel alone”, “I feel anxious”, “I feel irritated/angry”, “I feel sad”, “I feel that others don’t like me”* (respective loadings were 0.44, 0.43, 0.65, 0.72 and 0.71; Cronbach’s α = 0.6).

**Momentary psychotic experiences** were assessed using the mean score of three items: *“I feel like I have to be on my guard, that I'm not safe”, “I feel like my imagination is mixing with reality”, “I feel like I'm hearing or seeing things that other people don't perceive”* (respective loadings were 0.62, 0.65 and 0.77; Cronbach’s α = 0.43). This method was found to be a reliable measure of psychotic experiences (Feller, Ilen, Eliez, & Schneider, 2021)

**Stress**

To measure daily-life stress in different contexts, a similar approach to earlier studies was applied (Myin-Germeys et al., 2001). All items were measured on a scale from 1 (not at all) to 7 (extremely).

 **Social stress.** When participants reported being in company of others, they were asked to evaluate their subjective experience of this company. The mean score of following items was used to represent social stress (Cronbach’s α = 0.54): *“I would prefer to be alone”, “This company is pleasant”* (reversed score for analyses), *“I feel judged by this/these person(s)”, “I am nervous in the presence of this/these person(s)”.*

 **Activity stress.** At each beep, participants were asked to report their current activities. Based on their responses, we divided activities into six categories (adapted from Schneider et al., 2020): 1. Work/school; 2. House-related activities (housework, personal care): 3. Eating/drinking; 4. Social (social contact, online social contact); 5. Leisure (sport, other hobbies, TV, internet, rest); 6. Nothing. Participants were then asked to evaluate their current activity with following items: *“This activity is difficult”, “I enjoy doing this activity”* (reversed score for analyses). The mean score of these two items was used to represent activity-related stress (Cronbach’s α = 0.46).

 **Event stress.** Participants were asked to think about the most important event that happened since the last beep and report their subjective experience of this event. To measure event-related stress, the reversed score of the item *“This event was enjoyable”* was used in the analyses. Initially, we planned to add another item (i.e., *“This event was stressful”)* to the event stress measure but the internal consistency for these items was poor (Cronbach’s α = 0.39). Therefore, we decided to use only the item evaluating pleasure of past events that is more in line with what has been done in previous studies (e.g., Myin-Germeys et al., 2001). The first beep of the assessment was removed as the item referred to the previous beep, which had not yet occurred.

**Clinical evaluation**

To assess the presence of psychiatric disorders, the Diagnostic Interview for Children and Adolescents – Revised (DICA-IV) (Reich, 2000) or the Schedule for Affective Disorders and Schizophrenia for School-Age Children – Present and Lifetime version DSM-5 (K-SADS-PL-5) (Kaufman et al., 1997) were used with participants below 18 years old. Adults were assessed with the Structured Clinical Interview for Axis I DSM-IV/ DSM-5 (SCID) (Spitzer, Williams, Gibbon, & First, 1992). All the interviews were conducted by a trained child psychiatrist (SE). Psychiatric comorbidity was measured as the sum of current psychiatric diagnoses, in line with previous studies (Sandini et al., 2020).

**Deviations from the co-registration**

The following deviations from the co-registration should be noted: first, for the co-registration, the EMA variables were defined *a priori* but we decided to verify the internal consistency of the scales and perform a factor analysis to verify the loadings of items, which led to some modifications in the composition of the EMA variables. Second, because we assumed that the study would have been too large, we did not conduct analyses about the effect of social context for affects or social stress described in the co-registration, as they were not directly linked to our hypotheses. Third, we conducted a supplementary analysis about the possible effect of selective serotonin reuptake inhibitors (SSRIs) on the stress reactivity in the clinical group. Forth, when investigating the moderation effect of coping, we used LRT to assess model fit after adding a group to the model as a three-way interaction. Finally, as the distribution of the score of SIPS positive psychotic symptoms was positively skewed, we used Spearman rank correlations instead of regression models to examine the associations between stress reactivity and psychopathology. We also decided to include negative psychotic symptoms to our analyses to be able to investigate correlations between stress reactivity and not only positive but also negative symptoms.

1. **Results**

Possible effects of age and sex on stress in different contexts or on affective reactivity to different types of stressors were examined in the entire sample. No effects of either age or sex were observed. Results are reported in Table S1.

**Supplementary Table S1.** Effects of age and sex on stress and stress reactivity measures

|  |  |  |
| --- | --- | --- |
|  | **Age** | **Sex** |
|  | *β* (95 % CI) | *p* | *β* (95 % CI) | *p* |
| **Social stress** | 0.003 (-0.02 to 0.02) | 0.794 | -0.15 (-0.34 to 0.05) | 0.137 |
| **Activity stress** | -0.0008 (-0.03 to 0.02) | 0.953 | -0.18 (-0.39 to 0.03) | 0.09 |
| **Event stress** | -0.01 (-0.05 to 0.03) | 0.565 | -0.17 (-0.5 to 0.16) | 0.308 |
| **Social stress reactivity** | -0.003 (-0.03 to 0.02) | 0.786 | -0.08 (-0.29 to 0.13) | 0.435 |
| **Activity stress reactivity** | 0.008 (-0.002 to 0.02) | 0.106 | 0.05 (-0.03 to 0.13) | 0.229 |
| **Event stress reactivity** | 0.002 (-0.005 to 0.01) | 0.501 | 0.005 (-0.06 to 0.07) | 0.859 |

As almost half of our clinical participants had a diagnosis of anxiety disorder and a large proportion of them (*n*=15) used selective serotonin reuptake inhibitors (SSRIs) at the time of testing, an exploratory analysis about the effect of SSRI medication status on stress reactivity was conducted in the 22q11DS group. The effects of the duration and the dose equivalent of SSRI medication were controlled, together with age, gender and EMA period. No effect of medication status on stress reactivity was detected. Results are reported in Table S2.

**Supplementary Table S2.** Effect of stress x SSRIa interaction on negative affect, controlling for dose equivalent and duration of medication, age, gender and EMA period.

|  |  |
| --- | --- |
|  | **Outcome: negative affects** |
|  | *β* (95 % CI) | *p* |
| **Social stress x SSRI** | 0.14 (-0.07 to 0.36) | 0.192 |
| **Activity stress x SSRI** | 0.04 (-0.033 to 0.12) | 0.264 |
| **Event stress x SSRI** | 0.07 (-0.015 to 0.153) | 0.108 |

aSSRI status was determined on the basis of whether or not participants used SSRI medication at the time of testing; *n* = 15 clinical participants with and *n* = 22 clinical participants without SSRI medication.

Correlations between stress reactivity variables and psychopathology variables were investigated using Spearman rank correlations, controlling for the effects of age, sex, IQ and EMA period. Results are reported in Table S3.

**Supplementary Table S3.** Spearman rank correlation coefficients between stress reactivity and psychopathology variables in 22q11DS group, after controlling for age, sex, IQ and period

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
|  | **SIPS positive symptoms** | **SIPS negative symptoms** | **Total psychopathology** | **Internal psychopathology** | **External psychopathology** | **Psychiatric comorbidity** |
| **Social stress reactivity** | 0,505\*\*† | 0,516\*\* | 0,251 | 0,048 | 0,177 | 0,081 |
| **Activity stress reactivity** | 0,372\* | 0,200 | -0,141 | -0,24 | 0,008 | 0,25 |
| **Event stress reactivity** | 0,205 | 0,410\* | 0,018 | -0,010 | 0,141 | 0,347 |

\**p*<0.05, \*\**p*<0.01

†p-values surviving Benjamini-Hochberg correction (threshold = 0.0083)

Finally, the correlation analyses were repeated without univariate outliers (i.e., values >3SD of stress reactivity variables). The results are reported in Table S4.

**Supplementary Table S4.** Spearman rank correlation coefficients after excluding univariate outliers (social stress reactivity, *n*=1; activity stress reactivity, *n*=2) between stress reactivity and psychopathology variables, after controlling for age, sex, IQ and period

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
|  | **SIPS positive** | **SIPS negative**  | **Total** **psychopathology** | **Internal** **psychopathology** | **External** **psychopathology** | **Psychiatric comorbidity** |
| **Social stress reactivity** | 0,481\* | 0,551\*\* | 0,196 | 0,068 | 0,107 | 0,069 |
| **Activity stress reactivity** | 0,345† | 0,169 | -0,308 | -0,417\* | -0,077 | 0,113 |

†*p*<0.1, \**p*<0.05, \*\**p*<0.01

Note: p-values did not survive Benjamini-Hochberg correction

**References**

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