# Spatial attention impairments are characterized by specific electro-encephalographic correlates and partially mediate the association between early life stress and anxiety

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## Abstract

Although impaired attention is a diagnostic feature of anxiety disorders, we lack an understanding of which aspects of attention are impaired, the neurobiological basis of these impairments and the contribution of stressors. To address these gaps in knowledge, we developed and tested behavioral tasks designed to parse which subdomains of attention are more impaired with higher self-reported anxiety symptoms and used electro-encephalographic (EEG) recordings to probe the neural basis of attentional performance. Participants were *n*=57 individuals aged 18-35 with mild-to-moderate mood and anxiety symptoms. We took account of the COVID-19 pandemic as a naturalistic probe for prolonged stress occurring at a similar point in time for each participant. In these same participants, we assessed stressful events in early life prior to age 18 within discrete age brackets that may have a prolonged impact on neural functioning. Severity of anxiety was found to be specifically associated with impairments in spatial attention but not feature-based attention. Impairments in spatial *selective* attention were associated with decreased posterior alpha oscillations in EEG recordings, while spatial *divided* attention impairments were associated with a different profile of decreased fronto-central theta oscillations. These impairments in spatial attention also partially mediated the association between early life stressors and anxiety symptoms and were found to worsen as a function of prolonged current stress during the COVID-19 pandemic. Our results provide a thorough characterization of attention impairments associated with anxiety, their electro-encephalographic correlates and the impact of stressors both in early life and in adulthood.

# Introduction

Impairments in attention and concentration are a diagnostic criterion for anxiety disorders as well as for major depressive disorders (American Psychiatric Association, 2013). Although these impairments can be debilitating and disrupt day-to-day life (Jaeger et al., 2006), we do not yet know the exact nature of which types of attention are impaired with anxiety. We also do not yet understand the neurobiological basis of these impairments nor how they may be associated with and/or impacted by stressors. To unpack how attention becomes impaired with anxiety requires an understanding of the specific sub-types of attention that are affected, the neural basis of these sub-types and the impact of stressors on the association between attention and anxiety. To achieve these goals, we developed novel behavioral paradigms to assess subdomains of attention during electroencephalographic (EEG) recording and leveraged self-reports of stressors in isolated time windows during both early life and adulthood (the COVID-19 pandemic).

Goal-directed attention comes in many forms, but it is not yet known which forms are impaired with anxiety and which are spared. Selective attention refers to the ability to volitionally focus attention on goal-relevant information while ignoring distractions (Serences & Kastner, 2014) and can be further sub-divided into feature-based selective attention or spatial selective attention depending on whether the goal-relevant vs. distracting information is distinguished by feature (e.g., color) or location (e.g., left/right). Selective attention in particular is known to be associated with alpha oscillations (8-13 Hz) over cortical regions representing task-irrelevant or distracting information (Payne & Sekuler, 2014). For example, when asked to attend to stimuli in the right visual field while ignoring stimuli in the left visual field or vice versa, alpha oscillations are observed over posterior regions contralateral to the ignored visual field (Worden et al., 2000). Divided attention, another form of top-down attention, refers to situations in which one attempts to focus on two or more things at once (Cherry, 1953), and can be further subdivided into multi-tasking (e.g., cooking dinner while taking a phone call) or multiple sources (e.g., listening to music while also listening for one's name to be called outside a restaurant). Divided attention is associated with a slightly slower cortical oscillation known as theta (4-7 Hz) typically observed in fronto-central electrodes (Keller et al., 2017). In spite of the many decades of research into these various sub-domains of attention in cognitive psychology, we have yet to parse the specific sub-domains of attention that may become impaired in individuals with anxiety or their electroencephalographic correlates. Importantly, while prior research on attention in anxiety has primarily focused on characterizing the types of stimuli that drive anxiety (e.g., studies showing participants frightening images) and the ways that anxiety biases attention toward negatively-valanced stimuli (e.g., studies revealing a bias in attention toward angry or scared facial expressions in anxious individuals), many anxious individuals report difficulties with concentration even with neutral stimuli (e.g., reading books, participating in meetings, etc.). We therefore sought to explore the sub-types of attention that become impaired with emotionally-neutral stimuli.

To understand how stressors in both early life and adulthood impact the associations between attention impairments and anxiety, we took advantage of two types of stressors at isolated time points. First, we utilized self-reports of early life stress (ELS), also referred to as adverse childhood experience, which is known to be associated with increased prevalence of mood and anxiety disorders and psychopathology in adulthood (Afifi et al., 2008; Chu et al., 2013; Heim & Nemeroff, 2001; Kessler et al., 2010; van Nierop et al., 2018). Importantly, ELS has also been linked with cognitive impairments (Hedges & Woon, 2011; Pechtel & Pizzagalli, 2011) including sustained attention (Kambali et al., 2019; Wilson et al., 2012), working memory

(Majer et al., 2010; Saleh et al., 2017), and executive function (DePrince et al., 2009; Klaus et al., 2017). Despite these well-established associations, it remains unclear how ELS contributes to specific types of attention impairment with neutral stimuli in the context of anxiety. Moreover, it is not known whether attention impairments mediate the association between ELS and anxiety symptoms in adulthood. Second, to assess the impact of stress in adulthood, we used follow-up surveys collected on these same participants during the COVID-19 pandemic. We were able to leverage this opportunity to understand the impact of this widespread stressor on participants who had already undergone the aforementioned behavioral and EEG assessments on the order of 4-17 months prior. This allowed us to investigate associations between pre-pandemic attention impairments measured in the laboratory and mid-pandemic self-reports of anxiety and worsening concentration.

To parse the specific sub-types of top-down attention associated with anxiety symptoms, their electroencephalographic correlates, and the impact of ELS on attention and anxiety in adulthood, we took a multimodal approach. First, we designed behavioral paradigms using neutral stimuli aimed at unpacking the specific sub-domains of attention impaired in anxious individuals. Second, we used EEG recordings during attention task performance to delineate the neural correlates of these attention impairments. Third, we investigated associations among anxiety, attention, and stress using path analysis, and uncovered a mediation model showing that spatial attention impairments partially mediate the association between ELS and anxiety symptoms in adulthood. Additionally, using follow-up surveys collected on these same participants during the COVID-19 pandemic, we determined the associations between pre-pandemic attention and mid-pandemic anxiety and concentration difficulties. In line with the goals of the Research Domain Criteria (RDoC) approach (Insel et al., 2010), our multimodal measurements allowed us to link specific sub-types of attention across multiple units of analysis, including self-report, behavioral measures, and electro-encephalographic recordings.

# Methods

**Ethical Approval**

The Institutional Review Boards of Stanford University has approved this protocol (protocol #41837). A study coordinator thoroughly explains the protocol to participants and answers any questions before they can provide informed consent to begin the study. The study is conducted according to the principles of the Declaration of Helsinki (2008).

**Participants**

Participants between 18–35 years of age were recruited from the surrounding community and screened as part of a larger trans-diagnostic umbrella study (Tozzi et al., 2020). Briefly, participants were included who either reported at least a moderate degree of one or more of the following clinical phenotypes (anhedonia, anxious arousal, concentration problems, rumination, tension using established questionnaires) or who had no significant history of any psychiatric disorders. Participants were excluded for psychosis, mania, suicidal ideations representing imminent risk, substance abuse, or medical conditions interfering with ability to complete assessments. Participants were additionally excluded if taking any psychotropic medications for a mental health problem or if currently receiving therapy by a trained mental health professional. A total of $n = 57$ participants completed the study, including both symptomatic and asymptomatic participants matched in age and biological sex. Of these, $n = 54$ participants had complete self-report data and thus were included in analyses of symptoms and early life stress.

Demographic and clinical characteristics of the sample are depicted in Table 1 and Supplementary Table 1, respectively.

| **Demographic Characteristics** | **n (%)** |
|---|---|
| *Biological Sex* | |
| Female | 28 (49.12%) |
| Male | 29 (50.88%) |
| *Gender Identification* | |
| Female | 26 (45.61%) |
| Male | 30 (52.63%) |
| Other | 1 (1.75%) |
| *Education* | |
| Less than high school | 0 (0.00%) |
| Completed high school | 4 (7.02%) |
| Some college | 5 (8.77%) |
| 2-year college | 3 (5.26%) |
| 4-year college | 27 (47.37%) |
| >4-year college | 18 (31.58%) |
| *Race* | |
| Alaska Native | 1 (1.75%) |
| Asian | 20 (35.09%) |
| Black/African American | 3 (5.26%) |
| Pacific Islander | 1 (1.75%) |
| White | 35 (61.40%) |
| More than one race | 4 (7.02%) |
| Other | 3 (5.26%) |
| *Ethnicity* | |
| Hispanic or Latino | 14 (24.56%) |
| Not Hispanic or Latino | 43 (75.44%) |
| | **M (SD)** |
| *Age* | 27.40 (5.28) |

**Table 1. Demographic Features of the Sample.** *Abbreviations*: M = Mean; SD = Standard deviation; *Notes:* Percentages for race do not sum to 100% due to biracial reporting.

## Attention Tasks

Each participant performed the following four tasks in randomized order, designed to probe various sub-domains of attention. Each task was performed twice, with 30 trials each, once before and once during EEG recording. Participants reviewed the instructions for each task with the experimenter via PowerPoint to ensure full comprehension, and these instructions were reviewed just before beginning each task. For all tasks, participants were instructed to maintain fixation on a red dot at the center of the screen at all times. Each task, described in more detail below, utilized stimuli drawn from five object categories: faces, houses, cars, bodies, and pseudo-words (pronounceable words without semantic meaning). Each object stimulus was presented on a 10.5° phase-scrambled background generated from a different randomly selected image from the set (Bugatus et al., 2017). A summary of these tasks may be found in Figure 1.

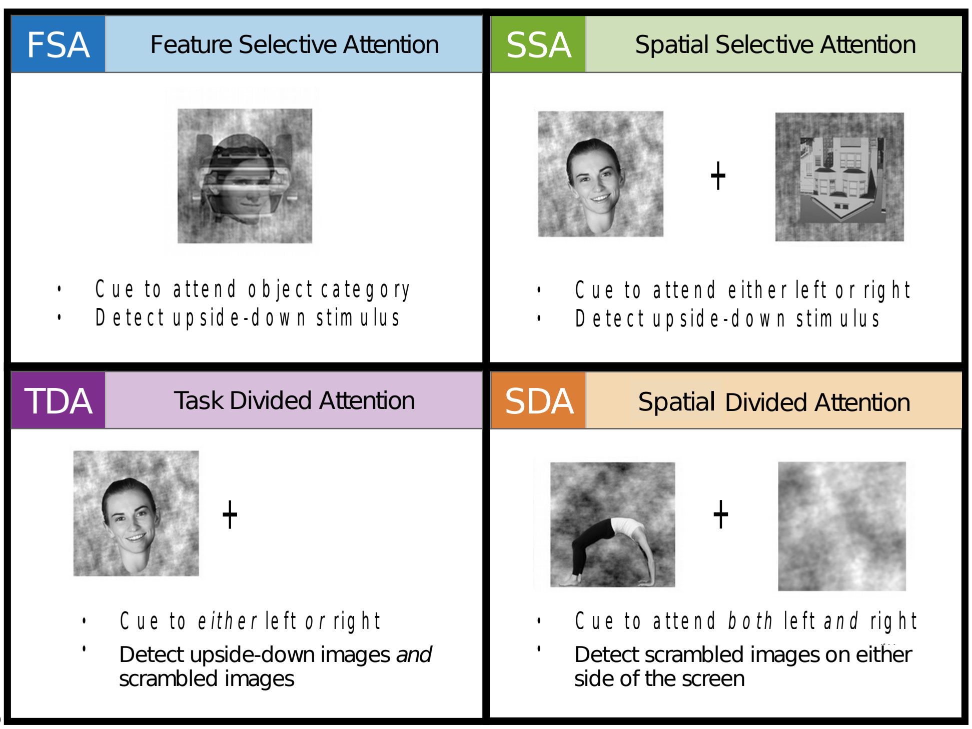


**Figure 1.** Behavioral attention task descriptions.

**<u>Feature-Based Selective Attention (FSA):</u>** To measure participants' ability to selectively attend task-relevant stimulus features while ignoring task-irrelevant features, we utilized a task developed in a prior study (Bugatus et al., 2017). In this task, participants are presented with 30 eight-second trials, each consisting of eight stimuli presented centrally for one second each. Each stimulus was composed of two overlaid images drawn from two different object categories (e.g. an image of a face superimposed on an image of a house). Participants were instructed to attend to a particular object category on each trial and to make a button press when they detected an upside-down stimulus in the attended category. Responses were to be withheld for upside-down stimuli in the ignored category. Each trial began with a cue to attend a particular object category (e.g. “faces”) followed by eight stimuli containing overlaid images from this cued category overlaid with images from another, ignored, object category (e.g. houses).

**Spatial Selective Attention (SSA):** To assess each participants’ ability to selectively attend one region of space while ignoring task-irrelevant regions, we modified the FSA task described above. In this version, we presented two spatially-separated (non-overlaid) images at a time, one to the left of fixation and the other to the right of fixation. Instead of cueing participants to attend to a particular object category, we cued participants at the beginning of each trial to attend to either the “left” or the “right” side of the screen. We instructed participants to make a button press when they detected an upside-down stimulus on the attended (cued) side of the screen while ignoring upside-down images on the un-cued side. Importantly, participants were to utilize covert attention (shifting focus to one side or the other without a corresponding shift in eye gaze) by instructing participants to maintain fixation on the red dot in the center of the screen. Each trial of eight stimuli consisted entirely of images drawn from a single object category.

**Task Divided Attention (TDA):** To measure how well participants could divide their attention among multiple tasks (referred to colloquially as “multi-tasking”), we modified the paradigm described above to require participants to perform two tasks simultaneously. On each trial, we presented eight images from one object category at a time, either on the left or the right side of the screen (without competing stimuli on the opposite side). Participants were instructed to make one type of button press ("1") whenever they detected an upside-down stimulus and to make a different type of button press ("2") whenever they detected a phase-scrambled image with no object.

**<u>Spatial Divided Attention (SDA):</u>** To measure participants' ability to divide their attention simultaneously among sources of sensory information while performing only a single task, we again modified the paradigm described above. In this version of the task, participants were instructed to simultaneously pay attention to two streams of stimuli, one on each side of the computer screen, and to respond with a button press whenever a scrambled image was detected on *either* side of the screen. This task necessitated the use of divided attention among sources of information because the target scrambled image could occur on either side of the screen, so to perform the task optimally participants needed to monitor both streams of information simultaneously.

**EEG Recording**

Electroencephalographic (EEG) signals were recorded from the scalp using a high-density, 129-electrode array (Electrical Geodesics, Inc.) and high-impedance amplifiers. All channels were adjusted for scalp impedance <50 kΩ at the beginning of the experiment and re-adjusted as needed halfway through the experiment. Signals were sampled at 250 Hz with a 0–100 Hz analogue bandpass filter and stored for offline analysis. Bipolar periocular channels were recorded from above and below each eye, and from a location near the outer canthus of each eye.

EEG signals were preprocessed using the EEGLAB toolbox (Delorme & Makeig, 2004) for Matlab (Mathworks). The recorded signals were re-referenced to the grand average. A 0.25 Hz Butterworth high-pass filter and a 60 Hz Parks-McClellan notch filter were applied. Eye blinks were identified by visual inspection of independent component analysis (ICA) and eliminated. Epochs containing muscle artifacts or saccades, identified through ICA and visual inspection, were rejected. Wavelet analysis and plotting were performed using the FieldTrip Matlab toolbox 2013-10- 24 (Oostenveld et al., 2011).

In accordance with prior work (Keller et al., 2017), we hypothesized that selective attention would be associated with stimulus-independent (induced) posterior alpha oscillations while divided attention would be associated with fronto-central theta oscillations. We therefore computed time-frequency representations using Morlet wavelets with a width of 4 cycles per wavelet at center frequencies between 1 and 70 Hz, in 1 Hz steps. For analyses of induced alpha oscillations, we first removed stimulus-evoked responses by subtracting out the event-related potential (Deiber et al., 2009; Tallon-Baudry & Bertrand, 1999). We then calculated wavelet theta (4-7 Hz) and alpha (8-13 Hz) power for our a priori electrodes of interest (O1 and O2 for alpha oscillations, and FCz for theta oscillations) during epochs extending from 600 ms prior to stimulus onset through 1600 ms after the onset of a sequence, before selecting narrower time epochs for analysis. Power values for theta and alpha oscillations were log transformed in order to better approximate a normal distribution.

**Self-Report**

*Composite Inattention Score*

Historically, questionnaires assessing symptoms of depression and anxiety disorders have had limited coverage of items relevant to the diagnostic feature of concentration problems that is common to these disorders. For the present study we followed a face validation process to operationalize attention impairments based on item-level questions assessing attention and concentration impairments contained with previously validated symptom measurements that were available within the umbrella study sample. Consistent with the definition of face validity as the degree to which a psychological item appears effective in terms of its stated aims, we selected four items that asked about how well participants perceived themselves as able to pay attention or concentrate, re-coded one item for consistent directionality such that higher scores represent worse inattention, and then averaged these items to form a composite inattention measure. These items assessed self-reported problems with "Concentration/Decision Making", degree of agreement with the statement "I don't 'pay attention'", degree of agreement with the statement "I concentrate easily" and endorsement of "Trouble concentrating on things, such as reading the newspaper or watching television" and were correlated with one another between 0.49. These items, their respective questionnaires and the coding scheme used are reported in Supplementary Table 2. The internal consistency of these items, quantified by the Chronbach's Alpha reliability statistic (Cronbach, 1951), was 0.835 which is considered good (Tavakol & Dennick, 2011).

*Depression and Anxiety Symptoms*

To assess symptoms typical of anxiety and related mood disorders, participants completed the full version of the Depression Anxiety and Stress Scales (DASS), a 42-item instrument that yields dimensional measures of depression, anxiety and stress that do not directly reflect diagnostic categories but rather symptom features that are present across the normative through clinical range in the population  (Lovibond & Lovibond, 1995). The DASS is normed for samples that include this full range (Psychology Foundation of Australia, 2018) and has been validated for a wide representation of samples and backgrounds (Daza et al., 2002; Jun et al., 2018; Tonsing, 2014; Tran et al., 2013; Vignola & Tucci, 2014; Wang et al., 2016).

We assess all three DASS scales, and our working hypotheses focus in particular on the Anxiety and Stress scales.  The Anxiety scale assesses autonomic and physiological signs of anxiety (e.g., "I experienced breathing difficulty" and "I sweated noticeably in the absence of high temperatures or exertion" associated with fear-related anxiety disorders (Psychology Foundation of Australia, 2018) and that we have defined previously as anxious arousal (Grisanzio et al., 2018).  The Stress scale assesses symptoms associated with generalized anxiety disorder (e.g., "I found myself getting upset rather easily" and "I found it hard to wind down" (Lovibond & Lovibond, 1995),  and that we have previously referred to as "general anxiety" for application outside of a diagnostic context (Grisanzio et al., 2018). Given that the Anxiety scale assesses symptoms associated with the physiological manifestations of anxiety, while the Stress scale assesses symptoms akin to those of generalized anxiety, we will hereafter refer to these scales as "physiological anxiety" and "generalized anxiety" respectively.

*Early Life Stress*

Exposure to early life stress between 0 and 17 years of age was assessed using the Early Life Stress Questionnaire (ELSQ) (Chu et al., 2013; McFarlane et al., 2005). The ELSQ is scored dichotomously for the presence/absence of exposure to specific early life stressors known to be traumatic or highly stressful and asks participants to report the age bracket(s) in which these events occurred: 0-3 years old, 4-7 years old, 8-12 years old, or 13-17 years old.

*Symptoms During the COVID-19 Pandemic*

Of our *n*=57 participants, *n*=29 completed a set of follow-up surveys during the COVID-19 pandemic, between 140-491 days after the initial experiment. These surveys included the DASS-21, an abbreviated version of the DASS-42 used in the initial experiment with the same scales for depression, physiological anxiety and generalized anxiety, as well as a general survey including items about concentration: “Did you start experiencing concentration problems due to the pandemic?” and “How have your concentration problems changed due to the pandemic?”

**Statistical analysis**

Linear regressions were used to assess the relationships among behavioral measures, self-report, and electroencephalography. All regression analyses included age and biological sex as covariates, and analyses comparing pre-pandemic symptoms to mid-pandemic symptoms included a covariate for the time elapsed between assessments. T-tests were used to compare behavioral reaction times in participants with either high or low composite inattention scores (median split). Statistical analyses were performed in Matlab R2020a and *R* version 4.0.3 with RStudio version 1.3.1093.

# Results

**Composite inattention scores are associated with spatial attention impairment.**

To parse the specific sub-type of attention associated with self-reported inattention symptoms, we used a composite inattention score comprised of items from several surveys. Using a median split on these composite inattention scores, we found that those with worse composite inattention had slower reaction times on the SSA task while those who reported better attention exhibited faster reaction times ($t(54)$= 2.669, $p$=0.010; Figure 2). A similar trend was observed for reaction times on the SDA task ($t(54)$= 1.050, $p$=0.085; Figure 2). Self-reported composite inattention scores were not significantly associated with performance on any other behavioral task ($p$s>.05).

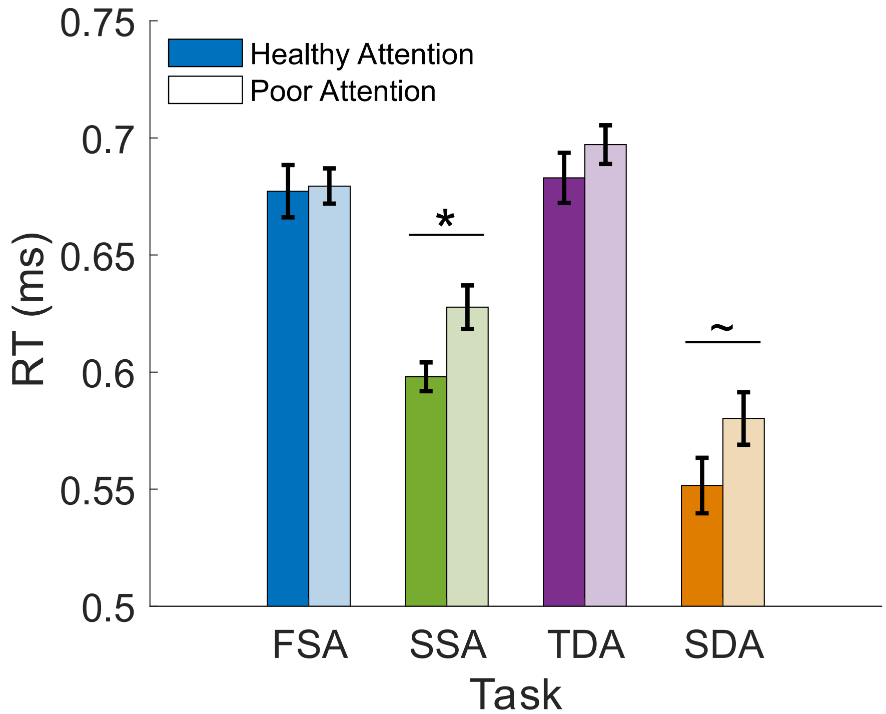


**Figure 2.** Composite inattention scores are associated with slower spatial selective attention reaction times. Reaction times depicted separately for those with composite inattention scores below the median (dark bars) and above the median (light bars). Error bars represent standard error of the mean. *Abbreviations:* FSA: Feature-based selective attention; SSA: Spatial selective attention; TDA: Task divided attention; SDA: Spatial divided attention; RT: Reaction time. *$p<0.05$; ~$p<0.1$.

**Spatial attention impairment is associated with anxiety but not depression.**

To determine whether impairment on tasks assessing specific sub-types of attention were associated with higher symptom severity on scales of the DASS, we used linear regressions to compare reaction times with self-report scores after accounting for age and biological sex as covariates (Table 2). We found that reaction times on the spatial selective attention task were associated with severity of both physiological anxiety (β=52.854, *p*=0.011) and generalized anxiety (β=76.238, *p*=0.007) after accounting for covariates, with the generalized anxiety association surviving strict Bonferroni correction for multiple comparisons. Reaction times on the spatial divided attention task were significantly associated only with severity of physiological anxiety (β=38.133, *p*=0.017). There were no significant associations with the depression scale for any of the attention tasks highlighting the specificity of the observed associations with anxiety.

| Attention Task | Symptom Subscale | N | Estimate | Std. Error | *t* value | *p* |
|---|---|---|---|---|---|---|
| FSA | Depression | 54 | 16.781 | 36.412 | 0.461 | 0.647 |
| | Physiological Anxiety | 54 | 19.762 | 21.086 | 0.937 | 0.353 |
| | Generalized Anxiety | 54 | 4.436 | 29.112 | 0.152 | 0.880 |
| SSA | Depression | 54 | 10.973 | 36.615 | 0.300 | 0.766 |
| | Physiological Anxiety | 54 | 52.854 | 20.013 | 2.641 | 0.011* |
| | Generalized Anxiety | 54 | 76.238 | 27.185 | 2.804 | **0.007**** |
| TDA | Depression | 54 | 5.115 | 35.857 | 0.143 | 0.887 |
| | Physiological Anxiety | 54 | 21.004 | 20.694 | 1.015 | 0.315 |
| | Generalized Anxiety | 54 | 30.844 | 28.286 | 1.090 | 0.281 |
| SDA | Depression | 54 | 17.369 | 27.914 | 0.622 | 0.537 |
| | Physiological Anxiety | 54 | 38.133 | 15.419 | 2.473 | 0.017* |
| | Generalized Anxiety | 54 | 33.280 | 21.860 | 1.522 | 0.134 |

**Table 2.** Comparison of attention task reaction times with depression, anxiety, and stress scales of the DASS. *Abbreviations:* FSA: Feature-based selective attention; SSA: Spatial selective attention; TDA: Task divided attention; SDA: Spatial divided attention; DASS: Depression, Anxiety and Stress Scales. *$p<.05$; **$p<.01$. Boldface font represents *p*-values passing Bonferroni correction for multiple comparisons.

**Early life stress is associated with poorer spatial attention and depression and anxiety symptoms in adulthood.**

Consistent with prior literature, we found that the total number of reported early life stressors was significantly associated with symptom severity in adulthood on all three scales of the DASS, as depicted in Table 3. Stressful events occurring at 4-7 years had the largest effect on the depression scale ($\beta$=4.682, $p$<.001) while stressors occurring at 13-17 years had the largest effect on both physiological ($\beta$=3.335, $p$<.001) and generalized anxiety ($\beta$=3.746, $p$<.001).

Given our finding that physiological and generalized anxiety in adulthood are associated with poorer spatial attention, we were next interested in understanding whether these spatial attention impairments are more common in those with a history of ELS. We found that the total number of early life stressors was marginally associated with poorer spatial selective attention ($\beta$=0.004, $p$=0.069) and significantly associated with poorer spatial divided attention ($\beta$=0.007, $p$=0.010) as measured by reaction times on the SSA and SDA tasks respectively (Supplementary Table 3). These associations were strengthened when we looked specifically at ELS occurring in ages 13-17 (SSA: $\beta$=0.015 $p$<.001; SDA: $\beta$=0.016, $p$=.006).

| Early Life Stress | Symptom Subscale | N | Estimate | Std. Error | *t* value | *p* |
|---|---|---|---|---|---|---|
| Total Count | Depression | 54 | 2.002 | 0.478 | 4.191 | **1.13e-04*** ** |
| | Physiological Anxiety | 54 | 1.481 | 0.247 | 6.001 | **2.18e-07*** ** |
| | Generalized Anxiety | 54 | 1.765 | 0.366 | 4.819 | **1.38e-05*** ** |
| Ages 0-3 | Depression | 54 | 2.331 | 2.109 | 1.105 | 0.274 |
| | Physiological Anxiety | 54 | 1.133 | 1.234 | 0.918 | 0.363 |
| | Generalized Anxiety | 54 | 2.298 | 1.672 | 1.375 | 0.175 |
| Ages 4-7 | Depression | 54 | 4.682 | 1.084 | 4.320 | **7.4e-05*** ** |
| | Physiological Anxiety | 54 | 1.500 | 0.709 | 2.115 | 0.039* |
| | Generalized Anxiety | 54 | 1.680 | 0.985 | 1.705 | 0.095 |
| Ages 8-12 | Depression | 54 | 3.372 | 1.497 | 2.253 | 0.029* |
| | Physiological Anxiety | 54 | 2.953 | 0.815 | 3.623 | **6.8e-04*** ** |
| | Generalized Anxiety | 54 | 3.578 | 1.147 | 3.120 | **0.003** ** |
| Ages 13-17 | Depression | 54 | 2.352 | 1.124 | 2.092 | 0.042* |
| | Physiological Anxiety | 54 | 3.335 | 0.494 | 6.745 | **1.51e-08*** ** |
| | Generalized Anxiety | 54 | 3.746 | 0.771 | 4.860 | **1.2e-05*** ** |

**Table 3.** Association of early life stressors with mood/anxiety symptoms in adulthood. Symptom scales are derived from the DASS-42 self-report measure. *$p$<.05; **$p$<.01; ***$p$<.001. Boldface font represents *p*-values passing Bonferroni correction for multiple comparisons.

**Spatial attention impairments partially mediate the association between early life stress and anxiety symptoms in adulthood.**

We next sought to determine whether spatial attention impairments mediate the relationship between early life stress (ELS) and anxiety symptoms in adulthood. To do so, we used linear regressions with age and biological sex as covariates and assessed the change in the beta estimate for the association between ELS and self-reported physiological or generalized anxiety symptoms when attention impairments were added to the model. Our results, depicted in Figure 3, reveal that spatial selective attention impairments partially mediated the association between ELS and either generalized ($\beta_1$=1.765, $p$<.001; $\beta_2$=1.573, $p$<.001; Figure 3a) or physiological anxiety symptoms ($\beta_1$=1.481, $p$<.001; $\beta_2$=1.366, $p$<.001; Figure 3b) in adulthood. Similarly, spatial divided attention impairments partially mediated the association between the frequency of ELS and physiological anxiety symptoms in adulthood ($\beta_1$=1.481, $p$<.001; $\beta_2$=1.387, $p$<.001;

Figure 3c). All three of these mediation models were strengthened when we examined ELS occurring specifically in ages 13-17 years old (SSA/Generalized Anxiety: $\beta_1$=3.746, $p$<.001; $\beta_2$=3.349, $p$<.001; Figure 3d; SSA/Physiological Anxiety: $\beta_1$=3.335, $p$<.001; $\beta_2$=3.284, $p$<.001; Figure 3e; SDA/Physiological Anxiety: $\beta_1$=3.335, $p$<.001; $\beta_2$=3.185, $p$<.001; Figure 3f).

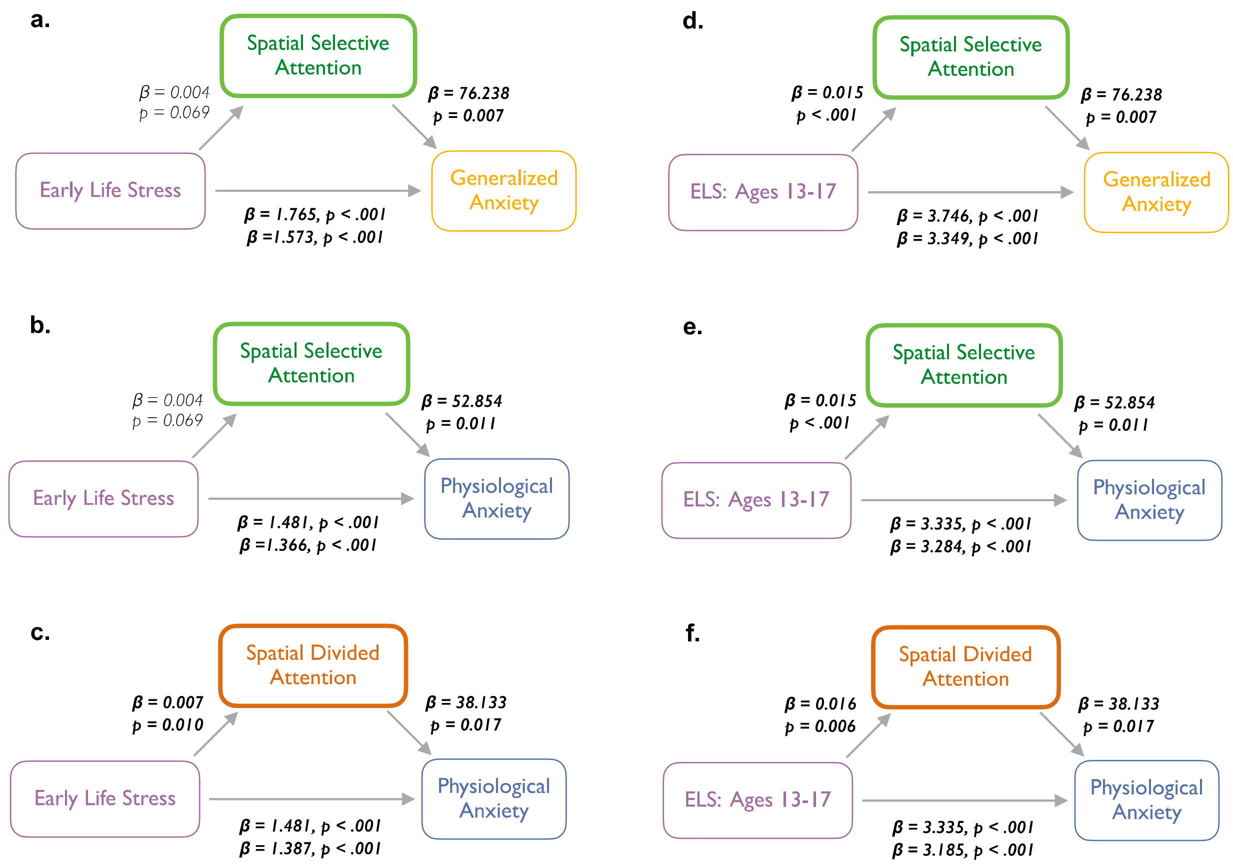


**Figure 3.** Mediation models depicting associations among early life stress, spatial attention behavioral performance, and stress/anxiety symptoms in adulthood. For associations between early life stress and anxiety symptoms, the β-value in the first row represents the association without including spatial attention, while the β-value in the second row represents the association with spatial attention included as a covariate. *Abbreviations:* ELS: Early Life Stress; SSA: Spatial selective attention; SDA: Spatial divided attention.

**Spatial selective attention is associated with posterior alpha oscillations, while spatial divided attention is associated with fronto-central theta oscillations**

As prior research has demonstrated distinct EEG correlates of selective and divided attention (Keller et al., 2017), we aimed to uncover EEG oscillations associated with spatial selective and spatial divided attention impairments in symptomatic adults. First, we investigated whether lateralized posterior alpha oscillations were associated with spatial selective attention reaction times. We found that left hemisphere posterior alpha oscillations were significantly associated with reaction times to target stimuli with attention cued to the left visual field ($\beta=-0.037$, $p=0.021$), consistent with the observation that alpha oscillations are associated with selective ignoring of task-irrelevant information (Payne & Sekuler, 2014). This effect was also observed between posterior alpha oscillations in the right hemisphere and reaction times to target stimuli with attention cued to the right visual field ($\beta=-0.024$, $p=0.047$). Second, we investigated the association between spatial divided attention and fronto-central theta oscillations. In line with our hypothesis, we found that higher fronto-central theta oscillations were associated with faster reaction times on the SDA task ($\beta=-0.031$, $p=0.040$). Results of these comparisons between hypothesized EEG oscillations and spatial attention task reaction times as well as time-frequency transforms of these EEG oscillations are depicted in Figure 4.

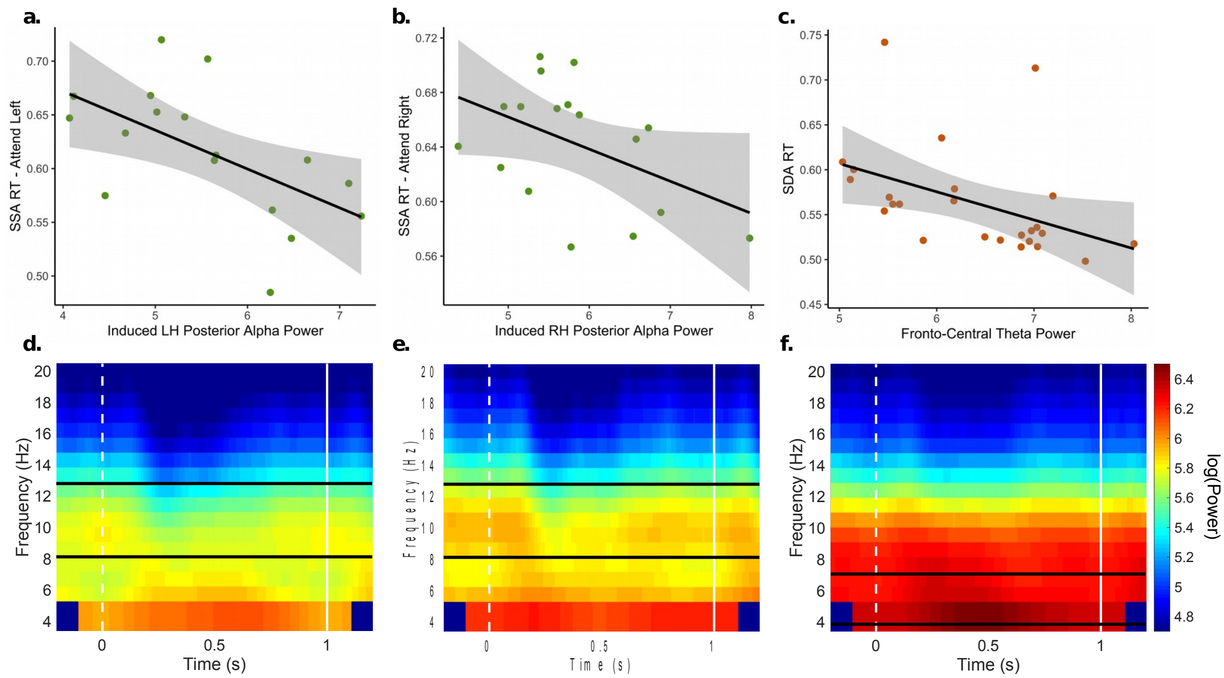


**Figure 4.** EEG oscillations associated with spatial selective attention (Panels a,b,d,e) and spatial divided attention (Panels c,f). Dashed white lines in Panels d, e, and f represent stimulus onset, while solid white lines represent stimulus offset. Solid black lines in Panels d, e, and f represent the hypothesized frequency bands for oscillations of interest: alpha (8-13 Hz) in Panels d and e; theta (4-7 Hz) in Panel f. *Abbreviations:* SSA: Spatial Selective Attention; SDA: Spatial Divided Attention; RT: Reaction Time; LH = Left Hemisphere; RH = Right Hemisphere.

**Spatial attention impairments and the COVID-19 pandemic**

During the COVID-19 pandemic, many individuals have experienced increased anxiety and difficulty concentrating. We therefore explored the role of pre-pandemic spatial attention impairments in predicting mid-pandemic anxiety and concentration. Given that our study was not powered to build robust predictive models to test on held-out data, we explored these associations in *n*=29 participants who completed follow-up self-report surveys during the COVID-19 pandemic.

Our results, depicted in Figure 5, show that pre-pandemic spatial selective attention impairments are significantly associated with physiological anxiety (β=53.740, *p*=0.039) and marginally associated with generalized anxiety (β=74.298, *p*=0.052) reported during the COVID-19 pandemic. Similarly, pre-pandemic spatial divided attention impairments are significantly associated with generalized anxiety (β=74.069, *p*=0.033) and marginally associated with physiological anxiety (β=41.971, *p*=0.083) reported during the COVID-19 pandemic. Importantly, we found that both physiological and generalized anxiety during the COVID-19 pandemic were significantly associated with worsening ability to concentrate during the pandemic with respect to pre-pandemic concentration (Physiological Anxiety: β=0.114, *p*<.001; Generalized Anxiety: β=0.086, *p*<.001).

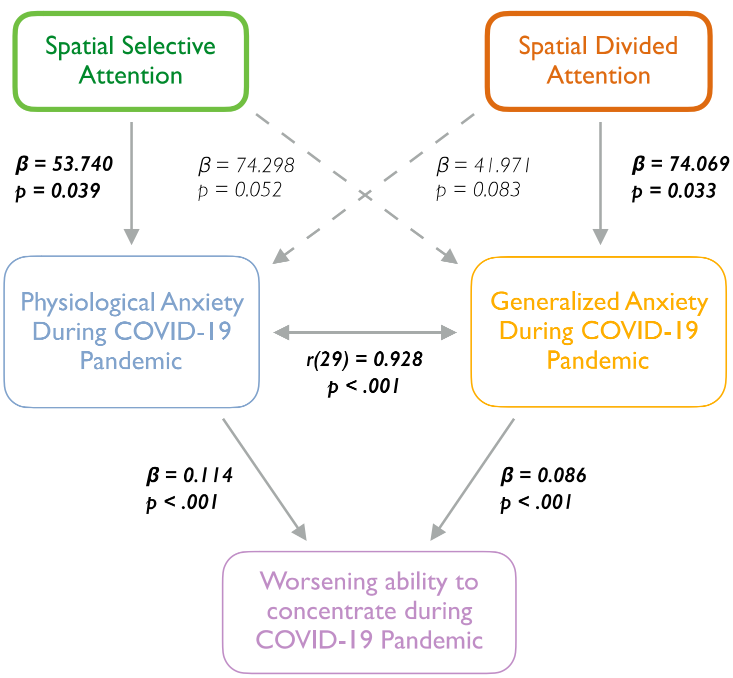


**Figure 5.** Associations between spatial attention, anxiety symptoms and concentration difficulties during the COVID-19 pandemic.

## Discussion

In this study we characterized attention impairments associated with anxiety using an approach that integrated multimodal measures of attention - self-reports of attention (concentration) problems, behavioral tasks designed to parse different subdomains of attention and EEG recordings to probe the neural correlates of performance on these tasks – and self-reports of different forms of anxiety – both physiological anxiety, characterized by autonomic and physiological signs of anxiety and generalized anxiety, characterized more by cognitive and affective indicators. We quantified the impact of two independent stressors - early life stressors self-reported at discrete developmental time windows, and the COVID-19 pandemic assessed by follow-up surveys - on these multimodal measures and report three key findings.

First, we demonstrated that behaviorally-assessed subdomains of spatial selective attention and spatial divided attention were associated with self-reported inattention and anxiety symptoms, but not depression symptoms. Second, we confirmed that these subdomains of spatial attention impairment are associated with distinct profiles of oscillations assessed by the EEG: specifically, spatial selective attention impairments were associated with decreased power of posterior alpha (8-13 Hz) oscillations contralateral to the ignored visual hemifield while spatial divided attention impairments were associated with decreased power of fronto-central theta (4-7 Hz) oscillations. Third, spatial attention impairments partially mediated the association between current anxiety symptoms in adulthood and the contribution of early life stress experienced at 13-17 years. Spatial attention impairments assessed pre-pandemic were associated with anxiety symptoms and reports of worsening concentration with the subsequent onset of the COVID-19 pandemic. These findings help to advance a more granular understanding of the associations between anxiety and attention and provide insight into how early life stressors and stressful situations in adulthood impact specific forms of attention.

Our finding that a dimension of generalized anxiety was associated significantly with behavioral performance on a spatial selective attention task builds upon prior mixed findings regarding whether or not anxiety is associated with spatial attention decrements (Carrasco et al., 2013; Kujawa et al., 2016; Ladouceur et al., 2006; Larson et al., 2013; Xiao et al., 2011). Prior studies reporting null findings have primarily used the Eriksen Flanker task (Eriksen & Eriksen, 1974) which often has ceiling performance (fast reaction times and near-perfect accuracy). While retaining accuracy is important for quantifying effects in the absence of performance variations, it may limit the opportunity for parsing aspects of spatial attention impairments that are more readily observed in a challenging task with a wider range of performance. Similarly, our finding that physiological anxiety is associated with behavioral performance on a divided attention task may build on mixed prior findings in adolescents (Gunther et al., 2005) older adults (Hogan, 2003) and college-aged participants (Hogan, 2003; Mialet et al., 1996). Our results suggest that the use of moderately challenging behavioral tasks allows a wider range of performance decrements and thus the opportunity to observe how decrements in selective and divided attention may increase along with increasing severity of anxiety symptoms. The specificity of the current findings to anxiety and not depression raises the possibility that anxiety may involve impairments in spatial attention in particular. Previously we have reported that depression implicates deficits in *feature-based* attention, and this possible dissociation of type of attention decrement by clinical features would be an interesting line of further enquiry.

Our second set of findings using EEG showed that spatial *selective* attention was associated with posterior alpha oscillations contralateral to the ignored visual hemifield, while spatial *divided* attention impairments were associated with fronto-central theta oscillations is consistent with observations in healthy adults (Keller et al., 2017). Numerous studies in healthy adults have shown an association between alpha oscillations and selective ignoring of task-irrelevant information (Payne & Sekuler, 2014). Other studies have shown that theta oscillations are associated with functions such as divided attention (Keller et al., 2017; McCusker et al., 2020), memory (Hsieh & Ranganath, 2014), and cognitive control (Cavanagh & Frank, 2014). Building upon these findings, our results show that spatial attention impairments in anxiety could take the form of either difficulty suppressing distracting information from task-irrelevant spatial locations or difficulty switching attention covertly between task-relevant spatial locations, with distinct electro-encephalographic correlates that mirror those observed in healthy adults.

Finally, our observation that attention impairments partially mediate the association between early life stress and anxiety in adulthood draws important connections between previously disparate lines of research. While it was previously known that early life stress is associated with both cognitive impairment (Pechtel & Pizzagalli, 2011) and anxiety (Chu et al., 2013), our findings provide a new indication that attention impairments may function as a potential mediator of the association between early life stress and anxiety. This mediation relationship suggests that a higher ‘load’ of stresses in early life may contribute to more severe anxiety in adulthood particularly when attention is disrupted. We might speculate that this relationship arises at least in part from common underlying mechanisms, that highlight the need for further investigation. For instance, early life stress has been shown to be associated with decreased power in multiple oscillatory frequency bands as measured by EEG, including both alpha and theta oscillations (McFarlane et al., 2005) consistent with our observations.

Attention impairments may also exacerbate anxiety symptoms in a number of ways. For example, an impaired ability to concentrate on everyday tasks while ignoring distractions could contribute to feelings of generalized anxiety such as worry (consistent with our observation that spatial *selective* attention impairment is associated with generalized anxiety symptoms), while having deficits in broader spatial awareness might contribute to feelings of anxious arousal (consistent with our observation that spatial *divided* attention impairment is associated with physiological anxiety symptoms), especially if one does not trust one's own ability to detect *where* a novel stressor might unexpectedly arise from as may be particularly the case with a higher load of ELS.

One advantage of our approach was our development of controlled laboratory measures to assess specific sub-types of attention behavior in our participants. Rather than treating attention as a unitary construct, we parsed the specific subdomains of attention that were impaired or spared in the context of anxiety symptoms. Future research may leverage these behavioral measures to further investigate attention impairment in anxiety or extend such work to other psychiatric populations. An additional advantage of our approach was the opportunity to assess stressors in both early-life and adulthood in discrete time-windows in order to uncover their associations with attention and anxiety. This allowed us to draw connections between early life stress, spatial attention impairment, and anxiety symptoms in adulthood, as well as to examine how the onset of a major stressor in adulthood impacts attention and anxiety symptoms.

Although our study had many strengths, made possible by the opportunity to acquire multiple measures in the same subjects, we were also faced with limitations. First, we focused on understanding correlations among our variables of interest rather than using causal manipulations. However, the onset of the COVID-19 pandemic yielded the opportunity to examine the impact of a major stressor on anxiety and attention in a pseudo-experimental manner using measurements before and during the pandemic in the same individuals. Moreover, prior studies have already performed causal manipulations of oscillations such as alpha and have demonstrated their direct impact on selective attention abilities (Romei et al., 2010) so future studies could investigate whether this same mechanism underlies selective attention impairments in clinical populations. Second, our COVID-19 follow-up survey data was collected only from a subset of individuals in our primary experiment who were interested in completing the follow-up survey, so we were relatively underpowered for these analyses. Our results from this small sample of subjects could be used to guide future studies with larger sample sizes to probe the interactions between stress, anxiety and attention.

Our development of behavioral laboratory measurements of attention impairment represents a first important step achieving a more precise characterization of the neurobiological dimensions that comprise such debilitating and prevalent disorders as anxiety. In particular, our study represents an important first stride toward characterizing the previously under-explored transdiagnostic symptom dimension of spatial attention impairments that is associated with greater severity of anxiety symptoms. This represents an important advance for both basic and clinical neuroscience by clarifying the specific subdomains of attention that are associated with affective dysfunction and their underlying neural correlates, as well as their interplay with stress in early life and adulthood.

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**Author Contributions:** A.S.K. and L.M.W. designed the experiment, A.S.K. and R.L. collected and preprocessed the data, A.S.K. undertook the analyses, and A.S.K., R.L., and L.M.W. wrote the paper.

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