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Common and specific dimensions of internalizing disorders are characterized by unique patterns of brain activity on a task of emotional cognitive control

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Abstract

Alterations in neural systems underlying cognitive control are well-documented across individuals with various internalizing disorders. The current study examined how individual differences in underlying traits related to internalizing disorders influence brain activation, as assessed by fMRI, when cognitive control must be exerted to make a decision about the emotional valence (positive, negative) of a task-relevant word displayed concurrently with a task-irrelevant emotional face. Taking a bi-factor model approach, fifty-five middle-aged female participants were characterized on symptom level on a common internalizing latent factor representing shared symptoms across anxiety and depression, as well as on specific factors remaining after taking the common internalizing factor into account: low positive affect, anxious arousal, and anxious apprehension. Contrasting activation on trials requiring higher vs. lower control revealed that higher levels of the Common Internalizing factor are associated with less deactivation of regions of the default mode network. Higher levels of the Low Positive Affect-specific factor are associated with less differentiation in engagement of portions of the fronto-parietal control network, while higher levels of the Anxious Arousal-specific factor are associated with less of a differentiation in activation of the thalamus. No effects were observed for level of the Anxious Apprehension-specific factor. These results suggest that prior findings of alterations in default mode activity associated with depression may not be specific to depressive symptoms per se but may characterize internalizing symptoms more generally. In addition, they suggest that reduced engagement of cognitive control regions may be more associated with low positive affect than depressive symptoms more generally.

1. Introduction

The goal of this paper is to understand alterations in neural systems involved in cognitive control as they are influenced by individual differences in dimensions of anxiety and depression in a community sample of adult women. This work is motivated by findings that internalizing disorders, which refer to a large category of psychopathology syndromes that generally includes primary dimensions of depression, worry, and fear (Achenbach & Edelbrock, 1978; Patterson, Mann, Grotzinger, Tackett, Tucker-Drob, & Harden, 2018), are debilitating and highly prevalent, especially among women: 30% of individuals in the United States develop Major Depressive Disorder and 42% develop an anxiety disorder within their lifetime (Kessler, Petukhova, Sampson, Zaslavsky, & Wittchen, 2012). Moreover, multiple avenues of research suggest that cognitive control mechanisms (i.e., mechanisms that allow for behavior to be organized in a goal-oriented manner, especially to override habitual actions or prepotent responses; e.g., Shallice, 1988) are altered or disrupted in individuals with a broad range of psychiatric disorders, including internalizing problems of anxiety and depression (for review see Snyder, Miyake, & Hankin, 2015) and are important contributors to impairments in social, occupational, and educational functioning (e.g., McIntyre et al., 2013). However, due to the high comorbidity of depression and anxiety (Kessler, Gruber, Hettema, Hwang, Sampson & Yonkers, 2008; Hankin, Synder, Gulley, Schweizer, Bijttebier, Nelis et al., 2016) it remains unclear which alterations in cognitive control are associated with the broad, comorbid symptoms expressed by individuals with internalizing psychopathology versus alterations that may be associated with specific dimensions of anxiety (e.g., anxious arousal, anxious apprehension) and anhedonic depression (low positive affect, loss of interest).

While much research has focused on diagnostic categories as defined by the DSM-5 (American Psychiatric Association, 2013), it is now widely understood that co- and multi-morbidities among disorders are extensive, and that psychopathology may best be conceptualized and modeled as latent dimensions to represent symptoms in a continuous manner, as opposed to discrete categorical disorders (e.g., Kotov, Krueger, Watson, Achenbach, Althoff et al., 2017; Lahey, Krueger, Rathouz, Waldman, & Zald, 2017). The tripartite model of anxiety and depression (Clark & Watson, 1991) characterizes depression and anxiety as having a common component of general distress marked by high negative affect. In addition, the model posits depression- and anxiety-specific components that are characterized by anhedonic depression and physiological hyperarousal, respectively (e.g., Clark & Watson, 1991; Watson, 2005). The tripartite model has been supported across many community and clinical samples (for review see Watson, 2005).

However, subsequent research has suggested that this model could be improved by distinguishing two distinct dimensions of anxiety, anxious arousal (i.e., panic) as suggested by the tripartite model, and a distinct form of anxiety known as anxious apprehension (i.e., worry) (Heller, Etienne, & Miller, 1995; Heller, Nitschke, Etienne, & Miller, 1997; Nitschke, Heller, Imig, McDonald, & Miller 2001; Sharp, Miller, & Heller, 2015). These two aspects of anxiety are associated with different patterns of brain morphology (e.g., Castagna, Roye, Calamia, Owens-Frach, Davis and Geening, 2017), different patterns of activity in specific brain regions (e.g, Engels, Heller, Spielberg, Warren, Sutton, Banich, & Miller, 2010), and differences in patterns of resting state connectivity (e.g., Burdwood, Infantolino, Crocker, Spielberg, Banich, Miller, & Heller, 2016).

Given these considerations, research has attempted to distinguish the neural substrates that are specifically associated with anhedonic depression, anxious arousal, and anxious apprehension, as they appear to be unique underlying factors that distinguish among manifestations of internalizing disorders. Much of this research has been performed in the context of measuring patterns of brain activity, either via functional magnetic resonance imaging (fMRI) or electroencephalography (EEG) under conditions in which cognitive control must be exerted.

To briefly summarize prior findings, increased levels of anhedonic depression are associated with decreased activation in left posterior dorsolateral prefrontal cortex (DLPFC) in the vicinity of the inferior frontal junction (Herrington et al., 2010; Silton et al., 2011), as well as increased levels of activation in dorsal anterior cingulate cortex (ACC) (Engels et al., 2010; Kaiser, Andrews-Hannah, Spielberg, Warren, Sutton et al., 2015), which likely reflects compensatory mechanisms for reduced DLPFC activity (Silton et al., 2011). As such, increased levels of anhedonic depression appear to be associated with alterations in activation in brain regions responsible for cognitive control when individuals must ignore emotionally-distracting information. In addition, increased levels of anhedonic depression are associated with increased activity in the posterior hub of the default mode network (i.e., posterior cingulate cortex), which might indicate increased attention to internal thoughts when, in contrast, it would be optimal to have attention directed outwardly (Kaiser et al., 2015).

Increased levels of anxious apprehension are associated with level of activity in left inferior frontal regions (Engels et al., 2007), which may reflect increased inner speech (the silent expression of conscious thought in a coherent linguistic form) that often accompanies worry. Finally, increased levels of anxious arousal are associated with activation in inferior regions of

the right temporal gyrus (Engels, et al., 2007), which has been suggested to reflect an exaggerated sensitivity to external stimuli that might cause alarm. As such, these studies suggest that individual differences in latent dimensions of psychopathology influence the ability to exert cognitive control in the face of emotionally-distracting information, and that these are reflected in variations in activation in portions of the fronto-parietal control network, limbic regions and the default mode network.

The goal of the present study is to extend the prior work in the following ways. First, we take a bifactor modeling approach that allows for the consideration of both common and specific dimensions relevant to internalizing psychopathology. Bifactor models parse symptom covariance into a common factor capturing what is shared across symptom dimensions, as well as multiple specific factors capturing what is unique to each symptom dimension. Recently, bifactor models have been applied to better differentiate the dimensions of the tripartite model, capturing what is shared across internalizing symptoms (Common Internalizing factor), and dimensions specific to anhedonic depression and anxious arousal. These models adequately fit internalizing symptoms (Lin et al., 2014) and demonstrate construct validity in relation to symptom, affect, and dysfunction measures (e.g., Simms, Grös, Watson, & O'Hara, 2008; Simms, Prisciandaro, Krueger, & Goldberg, 2012). However, these models have not included the important dimension of anxious apprehension, and have not yet been applied to understanding links between internalizing symptoms and cognitive control.

Here we take such an approach in which we identify a common internalizing factor, and then consider what additional and unique variance might be accounted for by low positive affect, anxious arousal and anxious apprehension (i.e., worry) (Snyder et al., in preparation). We then consider how each of these latent dimensions are related to cognitive control. In the prior studies

by Heller, Miller and colleagues, analyses focused on separable symptom dimensions (e.g., anhedonic depression, anxious arousal), and identified unique psychological and neural characteristics associated with each dimension. However, this approach did not systematically capture the broad, common internalizing dimension, which may have important and distinct associations with cognitive control. For example, Engels et al. (2010) found that levels of activation in DLPFC were altered in individuals with high levels of anhedonic depression but only when anxious arousal was also high, suggesting that this effect might reflect the influence of a common internalizing factor. Hence, to better model the relationship of common and unique dimensions of internalizing disorders to specific psychological and neural mechanisms, the current research simultaneously tested all dimensions with a bifactor approach.

Second, we further investigate whether the valence of distracting emotional information influences the nature and degree of cognitive control applied by individuals who vary in levels of symptoms related to these different emotional dimensions. In their prior studies, Heller, Miller and colleagues used an emotional Stroop task which required an individual to identify the color of the word while ignoring its meaning. Their results yielded important valence effects. For example, they observed a much larger response in left DLPFC to distracting words of positive rather than negative valence, an effect that was reduced for individuals high in anhedonic depression. In addition, they observed that while the amygdala response was greater to positive word than negative word distractors, this effect was amplified in individuals with depression (Herrington et al., 2010).

In the present research, we utilized an emotional Stroop task that involved a greater degree of direct competition between task-relevant and task-irrelevant information, more akin to the standard color-word Stroop. In the standard emotional Stroop task (Williams, Mathews, &

MacLeod, 1996), an emotionally salient, but task-irrelevant word (e.g., "suicide" in red ink) captures attention by engaging the word reading process as opposed to the main task of ink-color identification. While there is also competition between word reading and ink-color identification in the standard color-word Stroop task, there is, in addition, semantic competition between the word and ink color on incongruent trials (e.g., the meaning of the word "blue" and the meaning of the color "red") as well as competition between the response that would be selected for blue as compared to that selected for red.

To engender more extensive competition, the task in the current study was designed to be more analogous to the standard color-word Stroop task. In our task, individuals classified words as being positive in valence (e.g., "cheerful") as compared to negative in valence (e.g., "furious"), while viewing happy faces or angry faces. The use of stimuli that involve similar semantic processing on both task-relevant and task-irrelevant dimensions increases the level of competition and allows us to more powerfully examine the degree to which individual differences in the latent dimensions of internalizing psychopathology influence cognitive control. Moreover, the use of positive and negative information in both the task-relevant and task-irrelevant dimension allows us to examine valence-specific effects.

Finally, the prior studies were performed on emerging adult or younger adult samples (up to age 35; e.g., Silton et al., 2011). Here we focus on an older age group (35-65) composed of women. There were several reasons for this choice. First, the prevalence of anxiety and depression, whether as diagnosed disorders or elevated symptom levels, is considerably higher in women compared to men (Kessler, Chiu, Demler, Merikangas, & Walters, 2005). Second, it has become increasingly apparent that major aspects of brain development continue well into the mid-20s (e.g., Simmonds, Halquist, Asato and Luna, 2014), and the current study allows

investigation of associations of latent dimensions of internalizing psychopathology and cognitive control in a sample of more mature individuals. Lastly, this age range has been identified as an often overlooked but important period from the perspective of women's health.

With this extended design, there were a number of theoretical issues we wanted to evaluate. First, based on findings of broad compromise of executive function in individuals with depression (Snyder, 2013) and anxiety (Sharp, Miller, & Heller, 2015), one might predict that activation in regions involved in top-down attentional control implemented by the fronto-parietal network would likely vary with the degree of symptom related to a common internalizing factor, As such, the fronto-parietal network serves as a region of interest for the current study. However, the literature has identified executive deficits in depression more commonly than with anxious apprehension and anxious arousal (see Sharp, Miller, & Heller, 2015 for discussion), raising the possibility that executive deficits might be more specific to the dimension of anhedonic depression. In addition, the literature suggests alterations in activation of regions of the default mode network with both anhendonic depression and anxiety (Williams, 2017) but once again the generality of these effects across anhedonic depression and anxiety as compared to their specificity are not clear. As such, to examine this issue, the default mode network also served as a region of interest.

Second, based on the past literature in depressed individuals (e.g., Bogdan, Nikolova, & Pizzagalli, 2013; Zhang, Chang, Guo, Zhang, & Wang, 2013) one might predict that the specific dimension of anhedonic depression would be associated with alterations in activation in portions of the dorsal striatum (e.g. caudate, putamen) associated with executive aspects of reward – related processing (Balleine, Delgado, & Hikosaka, 2007), and that these effects would be especially pronounced for positively-valenced task-relevant or task-irrelevant information. We

were also interested in whether such effects might be observed in other portions of the brain involved in the processing of emotional information (e.g., limbic temporal regions).

Third, we wanted to investigate whether we would replicate prior work (Silton et al., 2010) suggesting that the specific dimension of anxious apprehension would be associated with alterations in activation in regions of prefrontal cortex that are associated with inner speech (e.g., inferior frontal gyrus). However, we were also interested in whether alterations would be observed in anterior portions of the prefrontal cortex involved in overall goal setting and planning, whose morphology we have previously observed in a young adult sample (approximate age of 30) to be associated with aspects of repetitive thought (Smolker et al., in preparation).

Fourth, we examined whether higher levels of the specific dimension of anxious arousal would be associated with greater activation in subcortical regions, such as the thalamus, which have been linked to arousal and can modulate processing by altering connectivity between cortical regions (Nakajima & Halassa, 2017) as well as parietal regions associated with autonomic arousal (Corbetta & Shulman, 2011; Heller, Nitschke, & Lindsay, 1997).

In addition, because both low positive affect and anxious apprehension may be associated with repetitive negative thoughts (although more likely about past events in the former case and about future events in the latter case; Watkins, Moulds, & Mackintosh, 2005; Hughes, Alloy, & Cogswell, 2008), we also considered the possibility that alterations in activity in the default mode network might be associated with higher levels of these two dimensions (e.g., Burdwood, Infantolino, Crocker, Spielberg, Banich et al., 2016). Finally, across the two dimensions of anxiety, we wished to examine whether higher levels of anxiety would be associated with more activity in the amygdala, as there is robust animal and human data linking alterations in amygdala activation with anxiety (e.g., Fox & Shackman, 2019). In addition, we examined

whether these effects are exaggerated when the task-irrelevant information is negative (i.e., angry in nature).

The results of these investigations is likely to have important implications. First, they may provide insights into how the level of internalizing psychopathology more generally influences patterns of brain activation when cognitive control must be exerted, as independent from the influence of levels of specific internalizing dimensions (i.e., low positive affect, anxious apprehension, anxious arousal). Second, they may provide information on how the valence of information, either positive or negative, differentially influences or engages cognitive control mechanisms across these dimensions. Such information would be useful as recent research suggests that some alterations in psychopathology may be valence specific. For example, work by Joormann and colleagues suggest that individuals with depression have a specific difficulty in disengaging attention from negatively-valenced as compared to positively-valenced information (e.g., Joorman & Gotlib, 2008).

2. Materials and Methods

2.1. Participants

Participants were 70 women aged 35-65 (M = 48.0, SD = 6.5), who are the parents of adolescents who also participated in our study (which is the subject of a separate report). Four participants were excluded due to low task accuracy on incongruent trials (<60%), two participants were excluded due to extensive signal dropout in frontal or temporal regions, two participants were excluded due to excessive movement (greater than 3mm), and two participants were excluded due to both excessive movement and low accuracy. An additional five participants did not have complete psychopathology measures, resulting in a final sample of 55 participants, all of whom were drawn from separate families. Families were drawn from an unselected community sample

originally recruited to participate in two different studies in the GEM (Genes and Environment Mood Lab, Benjamin Hankin, P.I.; for details of the two samples and studies, see Hankin et al., 2015; Snyder, Friedman, & Hankin, in press). These community samples were recruited from the Denver metro area, via public schools and using direct mail to target zip codes to maximize demographic and socioeconomic diversity. All parents of youth in the study were invited to participate, and the current sample represents those who agreed to do so. In addition, five fathers agreed to participate, but because their numbers were so low, they were not included in the present study.

The sample was not pre-screened on the basis of psychopathology, and thus represent the full dimensional spectrum of symptoms occurring in the general population. Lifetime depression and anxiety disorder diagnoses in the current sample were assessed with the Structured Clinical Interview for the DSM-IV (SCID) and were as follows: major depressive disorder 50.5% lifetime; generalized anxiety disorder 18.8% lifetime; social anxiety disorder 13% lifetime; panic disorder 4.7% lifetime. These lifetime prevalence rates for adult women are comparable to those reported in large epidemiological samples from the general community (e.g., Kessler et al., 2005). Mean levels of current symptoms assessed for the present analyses (Table 1) were very similar to other large community samples of adults for anhedonic depression and anxious apprehension (50^{th} percentile in comparison to Chirinos, Murdock, LeRoy, & Fagundes, 2017; Startup & Erickson, 2006), whereas anxious arousal scores were slightly lower (35^{th} percentile in comparison to Morozink, Friedman, Coe, & Ryff, 2010). Of the sample, only four individuals were currently taking psychotropic medication: 2 individuals were taking Venlafaxine, 1 was taking Fluoxetine, and 1 was taking Bupropion.

All participants were screened to be free of history of neurological insult. Demographic information on the sample is shown in Table 1. Informed consent was obtained from all participants and all procedures were approved by the University of Colorado Institutional Review Board.

Table 1. Demographics and scores on the PSWQ and MASQ of the sample.

Characteristic	**Mean (SD)**
Age (years)	48.19 (6.45)
WAIS Full Scale IQ	112.35 (12.3)
PSWQ	42.25 (11.49)
MASQ	
Anxious Arousal	19.42 (3.44)
Low Positive Affect (LPA)	39.75 (9.16)
Loss of Interest	11.64 (3.26)
Anhedonic Depression (sum of LPA and Loss of Interest)	51.38 (10.73)

2.2. Questionnaires used to characterize individual differences in levels of dimensions relevant to anxiety and depression

2.2.1 Mood and Anxiety Symptoms Questionnaire (MASQ). Anxious arousal and anhedonic depression were assessed with the MASQ (Watson et al., 1995), a 39-item self-report scale. It has been found to have good internal consistency, test-retest reliability, and convergent and discriminant validity in relation to depression and anxiety disorders (e.g., Nitschke et al., 2001; Watson, Clark, Weber, Assenheimer, Smith, Strauss, & McCormick, 1995; Watson, Weber, Assenheimer, Clark, Strauss, & McCormick, 1995). There are two anhedonic depression subscales: low positive affect (LPA; 14 items, e.g., "Felt like I was having a lot of fun" – reverse coded) and loss of interest (LI; 8 items; e.g., "Felt really bored"); LPA had high internal consistency in the current sample ($\alpha = 0.92$) and LI had acceptable internal consistency ($\alpha = 0.72$). The anxious arousal subscale (AAr; 17 items) assesses symptoms of panic and

physiological hyperarousal (e.g., "Hands were shaky"); it had acceptable internal consistency in the current sample ($\alpha = 0.71$).

2.2.2. Penn State Worry Questionnaire (PSWQ). Anxious apprehension was assessed with the PSWQ (Meyer, Miller, Metzger, & Borkoveck, 1990), a 16-item self-report questionnaire assessing tendency to worry (e.g., "My worries overwhelm me."). It has been found to have good internal consistency, test-retest reliability, and convergent and discriminant validity in relation to anxiety disorders (e.g., Brown, Antony, & Barlow, 1992; Molina & Borkovec, 1994). Internal consistency was high in the current sample ($\alpha = 0.93$).

2.2.3. Latent Variable Model

In order to have an adequate sample size for latent variable analysis, we took data from the current sample of adult women as well as others in the same study who completed the questionnaires but did not undergo neuroimaging and combined them with another community sample collected previously in the Urbana-Champaign, Illinois area by two of the authors of the current paper (Heller, Silton) (n = 117; 67.5% female; age M = 34.8, SD = 9.37, range 19-51) for a total combined sample of N = 204. See Supplemental Table 1 for demographics and descriptive statistics for the full combined sample. Models were fit on this combined sample and factor scores for participants in the current study extracted for use as covariates in the neuroimaging analyses.

Item parcels were created by averaging the items with the highest inter-item correlations to create four parcels per factor (PSWQ AAp = 4 item parcels, MASQ AAr = 4-5 item parcels, MASQ LPA = 3-4 item parcels, MASQ LI = 2 item parcels). Although there is debate about the pros and cons of item parcels versus individual items in factor analyses (e.g., Little, Rhemtulla, Gibson, & Schoemann, 2013; Marsh, Ludtke, Nagengast, Marin, & Von Davier, 2013), we used

item parcels in this case because of the relatively small sample size and large number of items (55 total): item parcels reduce the indicator-to-sample ratio and the number of parameter estimates, improving model stability and convergence (Little et al., 2013). Four item parcels were used because 3-4 indicators/factor is generally considered optimal for CFAs (Kline, 2015), and this approach ensured that the dimensions were equally represented (correcting for the fact that scales have different numbers of items). We used correlational parceling, which combines the most highly correlated items into parcels to create "mini-scales" that reduce the number of indicators to an optimal number, while preserving the construct structure (Little et al., 2013). Specifically, for each subscale, we first averaged pairs of items with the highest correlations, then averaged the 2-item parcels with the highest correlations to form 4-item parcels (except MASQ LI which was already at four indicators with 2-item parcels); in the case of scales with an odd number of items, remaining single items were averaged with the parcel they had the highest correlation with.

Confirmatory factor analysis was conducted in Mplus (Muthén & Muthén, 2012) using full information maximum likelihood estimation. As χ^2 is sensitive to sample size, good model fit was defined as: CFI>.95, RMSEA<.06 and SRMR<.08 (Hu & Bentler, 1999). A bifactor CFA was specified. Bifactor models are a statistical technique that accounts for the pervasive co-occurrence of psychopathology by parsing symptom covariance into a common factor capturing what is shared across symptom dimensions (e.g., common internalizing psychopathology), and unique, orthogonal, factors capturing what is specific to each symptom dimension (e.g., depression- and anxiety-specific factors). We selected a bifactor model for the current study because it allows us to disentangle the neural correlates of common and specific internalizing dimensions. Other models, such as hierarchical and correlated factor models, although

potentially equally valid representations of the data, do not enable separation of shared and specific variance for each symptom dimension (e.g., in a hierarchical factor model, the sub-factors still include common variance).

All parcels were specified to load onto the Common Internalizing factor that captures covariance across all indicators, and additionally onto their respective specific factors that represent the remaining unique covariance in each subscale after accounting for the common factor. Factors were constrained to be orthogonal to one another because what is shared between factors is already captured by the common factor (e.g., Chen, Hayes, Carver, Laurenceau, & Zhang, 2012). In an initial model including all four specific factors, loss of interest (LI) parcels had strong loadings only on the Common Internalizing factor, and there was no significant variance associated with the LI-specific factor, indicating the common factor fully accounted for covariance among the LI parcels. Thus, the LI-specific factor was eliminated, and LI parcels loaded only onto the common factor. In addition, modification indices suggested the need for residual correlations between one of the anxious apprehension (AAp) parcels and another anxious apprehension (AAp) and LI parcel.

This revised model had good to acceptable fit (CFI = .95, RMSEA= .067, SRMR = .070; χ^2 (90) = 172.28, p <.001), and all parcels loaded significantly on their factor(s). Factor scores were then saved for further analysis. Factor determinacies (a measure of the degree to which factor scores represent the true latent factors, >.9 is ideal) were high for the Common Internalizing (.91), LPA-specific (.91), and AAp-specific (.92) factors, but lower for the AAr-specific factor (.65). Hence, results involving the AAr factor scores should be interpreted with caution since the factor scores do not fully capture the true latent variable. The loadings for this model are shown in Figure 1.

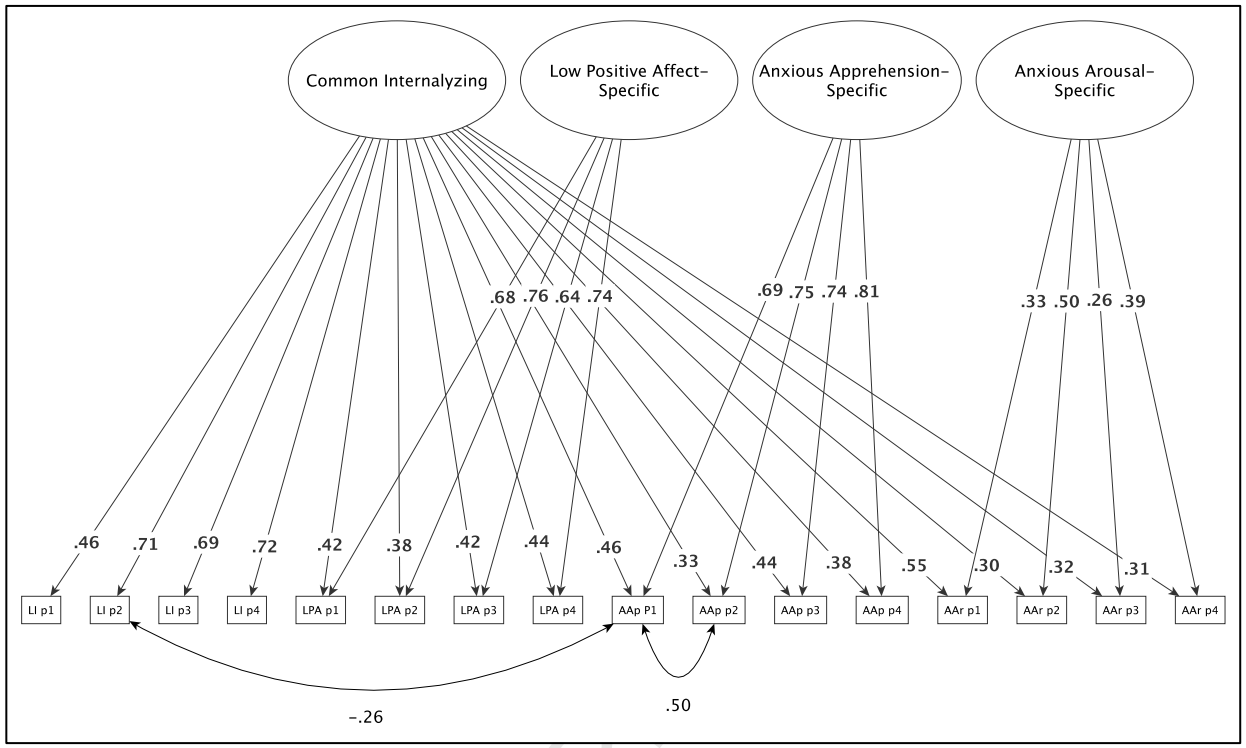


Figure 1. Loading of different item parcels on each of the latent factors. Notice that all parcels load on a Common Internalizing factor, while there are also loadings of specific parcels to each of Low-Positive Affect, Anxious Apprehension and Anxious Arousal.

2.3. Neuroimaging

2.3.1. Acquisition

Data were acquired on a Siemens PRISMA 3.0 Tesla scanner at the Intermountain Neuroimaging Consortium on the campus of the University of Colorado Boulder for all participants except for nine for whom data were acquired on the pre-upgrade version of the same magnet (TIM TRIO). Structural scans were acquired with T1-weighted sequence, with the following parameters: repetition time (TR)= 2400ms, echo time (TE)= 2.07ms, field of view (FOV)= 256mm, with a .8mm x .8mm x .8mm voxel size, acquired across 224 coronal slices. Functional scans were acquired using a sequence with the following parameters: TR= 460ms, TE= 27.2ms, FOV= 248mm, with a 3mm x 3mm x 3mm voxel size, acquired across 56 inter-

leaved axial slices and aligned along the anterior commissure-posterior commissure line. Two runs were acquired with each run consisting of a total of 624 echo planar images, for a total of 1248 images.

2.3.2. Stroop Task

The goal of this task was to identify those brain regions that are activated when cognitive control must be exerted in the face of semantic and response conflict between two categories of emotional items. Individuals made a semantic decision about whether words were positively-valenced (i.e., "cheerful", "joy", "happy", "delighted") or negatively-valenced (i.e., "furious", "mad", "angry", "rage"). The words were superimposed on three types of objects: faces with a happy expression, faces with an angry expression, and cars. Stimuli used in the present study were designed to be identical to those used with the adolescent offspring of the participants (which is the focus of another report.) As part of the goal in the adolescent sample was to examine the development of prefrontal-amygdala connectivity as assessed by fMRI, angry and happy faces were used as they show good reliability in this regard (Hallar, Kircanski, Stoddard, White, Chen et al., 2018). Cars, rather than neutral faces, were used as neutral stimuli because our prior work suggests that youth in the age range we tested show highly similar responses to faces with neutral and emotional expressions (e.g., Banich, Smolker, Snyder, Lewis-Peacock, Godinez et al., 2019).

Faces were drawn from the NIMSTIM database (Tottenham et al., 2009), using a set of 24 posers, with two angry expression and two happy expression images drawn from each poser. Thirty-two car images were drawn from the same larger set of images (Herzmann & Curran, 2011). Each poser was seen four times, twice in an angry and twice in a happy expression. For half of the trials, the word was placed in an upper position with regards to the object and on half

the trials it was placed in a lower position with regards to the object. Varying the position of the word made it less likely that an individual could narrow her focus of attention to just the central portion of the display where the word would appear so as to filter out the background image.

Three types of trials were constructed. On congruent trials, task-relevant words were drawn from the same semantic category (e.g., a positively-valenced word superimposed on a happy face). On incongruent trials the task-relevant word was drawn from the opposite semantic category than the task-irrelevant face (e.g., a negatively-valenced word superimposed on a picture of a happy face; a positively-valenced word superimposed on an angry face). On neutral trials, the task-irrelevant object was a car, which has no semantic or response relationship to either positively-valenced or negatively-valenced words. Each stimulus was displayed for a fixed period of 1380ms, followed by a fixed ITI of 480ms. Sample stimuli are shown in Figure 2.

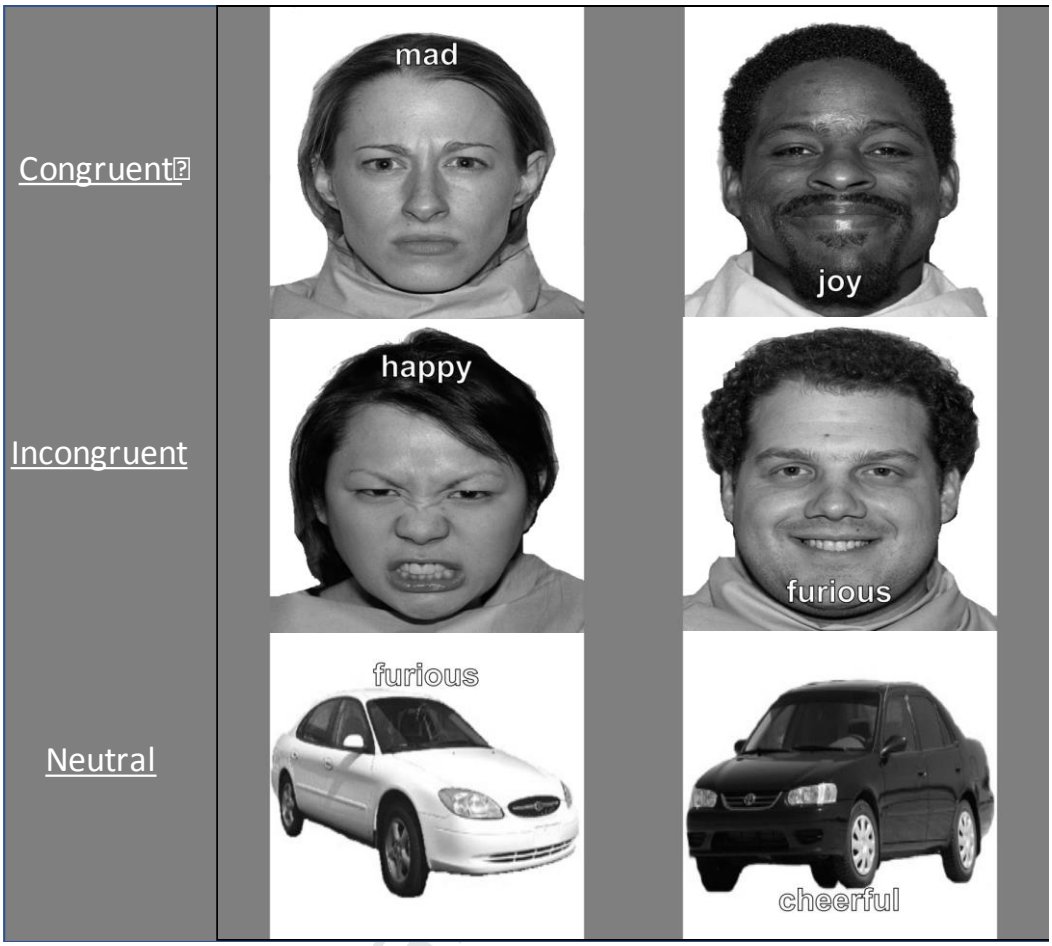


Figure 2. Examples of stimuli used in the current study. On each trial individuals viewed an item with an emotionally-valenced word superimposed on top of a picture which could either be a face of similar valence (congruent trials) or of different valence (incongruent trials) or a car (neutral trials).

Similar to designs used previously in our laboratory (Banich et al., 2009; Andrews-Hanna et al., 2011), this study was a mixed blocked/event-related design. Blocks consisted of trials that were on average, 2/3rds specific to that block (e.g., incongruent) and 1/3rd a set of neutral trials that were common across blocks, referred to as neutral frequent trials. In the neutral block, 2/3rds of trials were a set of neutral infrequent trials, and 1/3rd the same neutral trials that were common across blocks (i.e., neutral frequent). Six triads of blocks were created (e.g., INC, CIN) and these were flanked in a run by fixation blocks (F), that served as the baseline for the contrasts

discussed below. Each run consisted of three triads, so for example, a run might consist of FINCFNICFCIN. Two orders of blocks were employed, with button responses counterbalanced across subjects.

The exact number of trials per condition differed slightly. For half of the participants one of the congruent blocks contained 2/3rd frequent neutral trials and 1/3rd congruent trials, whereas the other half of subjects were presented with one of the incongruent blocks consisting of 2/3rd frequent neutral trials and 1/3rd incongruent trials. As a result, all subjects received a total of 216 trials, with half of the subjects seeing 44 incongruent and 48 congruent trials, and the other half seeing 48 incongruent and 44 congruent trials, with all subjects seeing 48 neutral infrequent and 76 neutral frequent trials.

2.3.2 Data analysis

2.3.2.1 Pre-Processing

fMRI preprocessing and analyses were carried out using the FSL suite (Smith et al., 2004). For the Stroop tasks, the first 10 EPI volumes of each run were discarded to allow the MRI scanner to reach steady-state stability. Preprocessing included motion correction via ICA-AROMA (Pruim et al., 2015), an independent component analysis method for removing motion, high-pass filtering (100 seconds), and BET brain extraction (Smith, 2002). Registration of EPI images into subject- and standard-spaces was executed using FLIRT (Jenkinson & Smith, 2001; Jenkinson, Bannister, Brady, & Smith, 2002). Individual subject EPI images were registered to that subject's MPRAGE structural image via linear Boundary-Based Registration (Greve & Fischl, 2009) and then registered to the MNI-152 template via 12 degrees of freedom linear transformation. The resulting EPI images were smoothed using an 8mm full-width half-maximum Gaussian smoothing kernel.

2.3.2.2. Blocked Analysis

As blocked analyses can have up to 35% more power than event-related analyses (Bandettini & Cox, 2000), we focus on using the more powerful blocked contrasts to investigate the covariation of individual differences in the expression of dimensions relevant to internalizing psychopathology. We have found in our prior studies that blocked contrasts in variants of the Stroop task enable individual differences to be detected (e.g., Banich et al., 2009; Andrews-Hanna et al., 2011).

We used FEAT within FSL to model the data. Our model had three EVs, one for each block type: incongruent, congruent, and neutral which modelled the time of the entire block (i.e., also including neutral frequent trials). Fixation blocks served as the non-modeled baseline. In addition, as in our prior studies, specific contrasts of interest were created. The first examined activity across all blocks compared to baseline (I+C+N>fixation) and reflected activity related to overall processing of the Stroop task. The second examined activity for incongruent and congruent blocks compared to baseline (I+C>N). This contrast isolates those regions that are engaged in cognitive control when information that could influence the decision is contained in both the task-relevant as well as well as task-irrelevant dimension of the stimulus, as compared to when it is only contained in the task-relevant word but not the task-irrelevant dimension, in this case, a picture of a car. The third contrast was of I>C which compares those trials in which information in the task-relevant and task-irrelevant stimulus dimensions conflict as compared to when they do not. Finally, we examined the contrast of I>N which compares those trials in which there is conflict in two competing sources of task-relevant information as compared to when there is no conflict or competing sources of information.

We ran two sets of analyses. The first focused on activation in the two networks of interest, the fronto-parietal network (FPN) and the default mode network (DMN). The second, which was performed to ensure that we did not miss any important findings outside of these networks, was a whole-brain analysis and exploratory in nature. For the former analysis we composed a mask that was the combination (i.e., additive sum; AND operation) of the two networks (FPN, DMN) of interest as derived from the publicly available maps of these networks from Yeo, Krienen, Sepulcre, Sabuncu, Lashkari, et al., 2011). In our main effect and covariate analyses, to guard against false positive results, we determined p values in a voxel-wise basis via permutation testing utilizing FSL's randomize tool with 10,000 permutations and set a voxel-wise threshold of $p<.0025$. We then employed cluster-wise correction using a family wise error (FWE) correction cluster threshold of $p<.05$ as determined by randomize within FSL based on a $p<.0025$ voxel-wise cluster forming-threshold. For the sake of completeness effects that passed voxel-wise correction with a cluster extent of 36 voxel or greater but which do not pass FWE correction are included in Supplemental tables 2-6.

We were also interested in activity in a variety of subcortical structures which, due to their smaller volume, might not pass cluster correction thresholds. As such, we examined activity in a variety of subcortical regions of interest (ROI) based on reports from meta-analyses across neuroimaging studies. One structure included was the amygdala because of its association with the processing of salient emotional materials, especially faces (Fusar-Poli et al., 2009) and alterations of its activity in anxiety disorders (Etkin & Wager, 2007). The striatum and thalamus were also included as ROIs because their activation is often altered in depression (Zhang et al., 2013). ROIs were defined via the Harvard-Oxford Subcortical Structural Atlas for each of these structures (e.g., caudate, pallidum, putamen, amygdala, substantia nigra, thalamus) in both

hemispheres. Activity that fell within these ROIs and was considered significant after the processes described above (permutation testing of 10,000 iterations with a voxel-wise threshold p<.0025) were included in the reported results even if they did not pass cluster correction threshold of 36 voxels or greater, as long as they had a cluster extent of at least 10 voxels.

2.3.2.3. Covariate models of individual differences in measures relevant to internalizing psychopathology

Because our bifactor model isolated four distinct factors - a Common Internalizing factor and three distinct specific factors (Low Positive Affect-specific, Anxious Arousal-specific, Anxious Apprehension-specific) - we ran each of the analyses described above four times with the analyses being distinguished by which factor scores were used as the covariate. As implemented in FEAT, factor scores across the sample were Z-transformed, and the Z value for each factor was entered as the covariate of interest in the GLM covariate analysis. In this analysis and those examining main effects, we also included a covariate of age, which for the current study was a variable of no interest. Corrections for multiple comparisons/false positives were performed as described above.

3. Results

3.1. Behavioral Results

The raw RT and accuracy data for the Stroop task are presented in Table 2. To control for individual differences in mean RT, we examined the percentage increase in RT on incongruent compared to congruent trials ((incongruent trials – congruent trials)/congruent trials) as our behavioral measure of interference. A one-sample t-test indicated significant RT interference (M= 4.99%, s.e. = .56%; $t(54)=8.56$, $p<.001$). Similarly, a paired-samples t-test indicated that accuracy was significantly higher for congruent as compared to incongruent trials ($t(54)=3.57$,

p<.001). These results are consistent with expected task performance and indicate that our task engendered cognitive control. As an exploratory analysis, we examined whether individual differences in behavioral performance were associated with factor loadings, but no robust effects were observed.

Table 2. Behavioral Performance for the different Stroop conditions. Numbers in parentheses are standard errors.

Emotional Stroop Task	Condition	Mean RT (ms)	Mean Acc (%)
	Congruent	790.88 (9.34)	96.75 (0.44)
	Incongruent	829.15 (8.91)	95.26 (0.51)
	Neutral	859.47 (9.56)	94.83 (0.61)

3.2. Neuroimaging Results

3.2.1 Effects Related to Cognitive Control – Main Effect

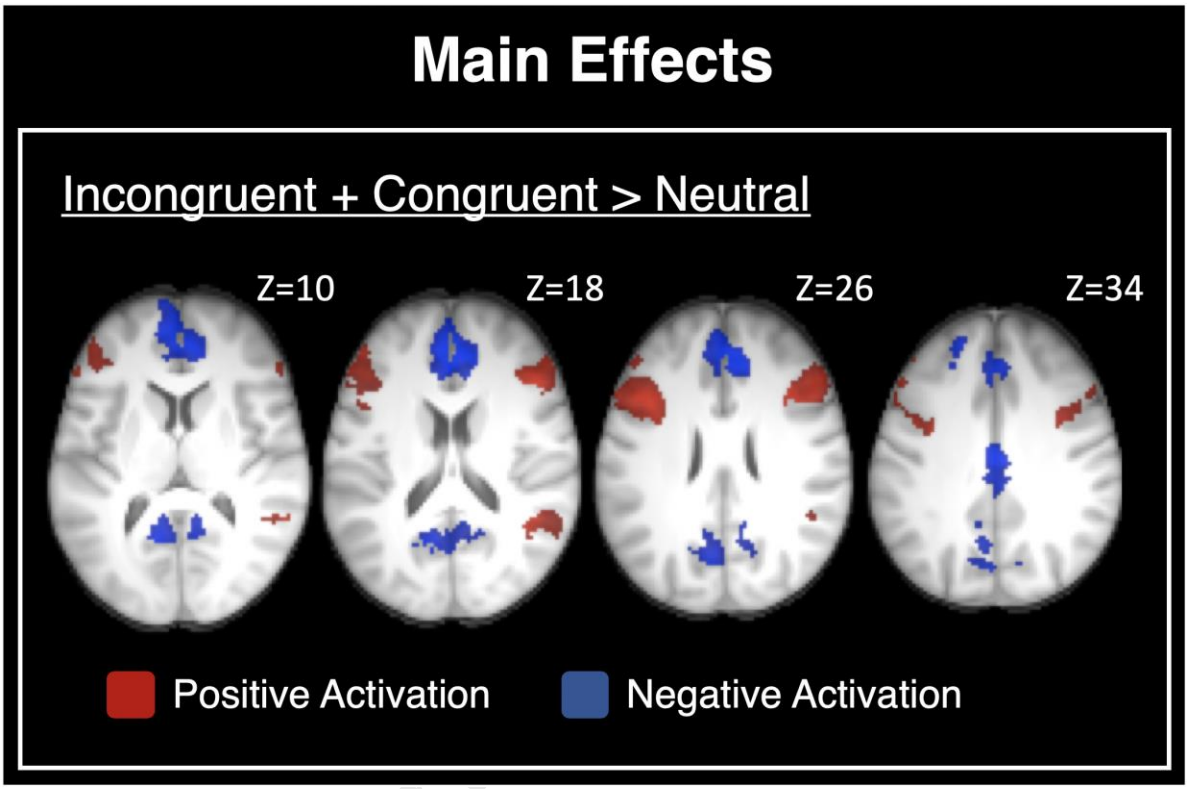
As expected, a contrast that serves as a proxy for the need for cognitive control (I+C>N) yielded extensive activation in regions of the fronto-parietal network bilaterally, including portions of the middle and inferior frontal gyrus (BA 46, BA 8) (see Table 3 and Figure 3).

Table 3. Regions showing Significant Effects for the Contrast of Incongruent + Congruent > Neutral Blocks.

Region	BA	Max Z	vox	x	y	z
Anterior_Cingulate(R)	BA32	-6.91	2639	6	40	20
Cingulate_Gyrus(L)	BA31	-7.06	1591	-2	-28	40
Middle_Frontal_Gyrus(L)	BA46	6.56	1360	-40	16	24
Middle_Frontal_Gyrus(R)	BA46	6.01	1077	48	26	20
Middle_Frontal_Gyrus(L)	BA8	-4.68	489	-20	24	44
Insula(R)	BA13	5.4	477	44	-22	-6
Superior_Temporal_Gyrus(R)	BA13	5.28	335	46	-46	14

BA = Brodmann Area; Max Z = Maximum Z value within cluster; vox=number of voxels; x, y, z, coordinates in MNI space. All effects passed voxel-wise correction at p<.0025 after 10,000 permutations and FWE cluster correction at p<.05 within the fronto-parietal and default mode network region of interest.

Figure 3. Brain regions that yielded significant activation across the group (i.e., main effects) for the contrast of incongruent and congruent trials greater than neutral trials. Regions depicted passed permutation testing at p<.0025 and FWE at p<.05 within the fronto-parietal and default mode network regions of interest. Areas yielding positive activation for the contrast are shown in red, while those yielding negative activation are shown in blue.



3.2.2. Effects Related to Cognitive Control - Covariate Results

3.2.2.1. Common Internalizing Factor

All significant associations of activation with level of the Common Internalizing factor are shown in Table 4 and Figure 4.

Table 4. Regions whose activation is significantly associated with level of the Common Internalizing factor.

Contrast	Region	BA	Max Z	vox	x	y	z
I >N							
	Superior Medial Frontal Gyrus(L)	BA 8	-5.12	299	0	50	36

I >C							
	Precuneus(L)	BA7	-5.09	487	-2	-74	48
	Inferior_Parietal_Lobule(L)*	BA39	-4.66	291	-40	-70	40
	%Thalamus (L)	N/A	-4.05	19	-8	-22	12
I+C>N	%Caudate (L)*	N/A	-3.88	10	-16	12	16
I+C+N>Fix	%Putamen(L)	N/A	-4.04	35	-18	8	6

BA = Brodmann Area; Max Z = Maximum Z value within cluster; vox=number of voxels; x, y, z, coordinates in MNI space; Effects listed passed voxel-wise correction at p<.0025 after 10,000 permutations and passed FWE cluster correction at p<.05 within the fronto-parietal and default mode network regions of interest except % which were subcortical areas of interest.*is not significant when evaluated using FLAME1+2 with outlier de-weighting selected

For the contrast of incongruent vs. neutral blocks, a higher score on the Common Internalizing factor was associated with less of a difference in activation between incongruent and neutral blocks in a portion of the superior medial prefrontal cortex. This area is considered part of the default mode network.

For the contrast of incongruent vs. congruent blocks, a higher score on the Common Internalizing factor was associated with less of a difference in activation in two cortical regions, both of deactivated for the group as a whole. Hence, a negative association indicates that more deactivation on incongruent as compared to congruent blocks is associated with higher levels of the Common Internalizing factor. The first region is a portion of the precuneus extending downwards into retrosplenial cortex and the second is a portion of the inferior parietal cortex, both of which are portions of the default mode network. In addition, a higher score on the Common Internalizing factor was associated with less a difference in activation between incongruent and congruent blocks in portions of the thalamus.

Finally, for the contrast of incongruent and congruent blocks compared to neutral blocks or all conditions compared to fixation baseline, a higher score on the Common Internalizing factor was associated with less activation in small portions of the caudate and putamen, respectively.

Because the distribution of scores on the common internalizing factor included one participant whose score could be considered an outlier (>4), we employed an additional method to evaluate the results. As noted in Mumford's (2017) review of methods, FSL's FLAME with outlier de-weighting is relatively robust at accounting for Type 1 errors (and is preferable to removing an outlier). Hence, to provide an additional examination of the data, we re-ran our analyses using FSL's FLAME 1+2 with outlier de-weighting with the same parameters as our initial permutation-based analysis (voxel-wise threshold $p<.0025$ and cluster correction at $p<.05$ within the combination mask of the frontoparietal and default mode networks) and examined the t-stat maps at a threshold of $p<.0025$. All of the effects observed using permutation testing remained significant except for the cluster in the inferior parietal lobule for the contrast of I>C and the activation in the caudate for the contrast of I+C>N.

In sum, higher levels of the Common Internalizing factor were associated with reduced activation/more deactivation on incongruent blocks, in contrast to either neutral blocks or congruent blocks, across regions associated with the default mode network.

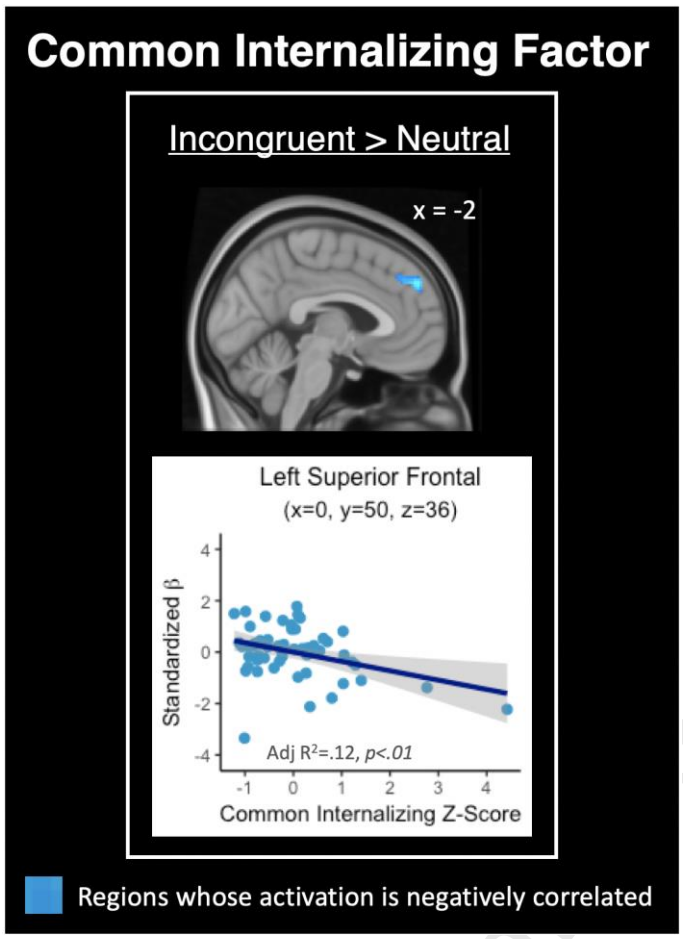


Figure 4. Brain regions whose activity is modulated by an individual's score on the Common Internalizing factor. Regions depicted passed permutation testing at a voxel-wise p<.0025 and FWE at p<.05 within the fronto-parietal and default mode network regions of interest. All regions exhibited a negative association with the factor and are shown in blue. Scatterplots show the relationship between an individual's Z score on the factor score and the standardized beta for a given brain region for the relevant contrast. The standardized beta was calculated via flsmeants for a 9mm diameter sphere centered at the relevant peak location listed in Table 5.

3.2.2.2. Low Positive Affect-specific Factor

A number of effects were observed in the relationship between brain activation and the level of the Low Positive Affect-specific factor (See Table 5 and Figure 5).

Table 5. Regions whose activation is significantly associated with the level of the Low Positive Affect-specific factor

Contrast	Region	BA	Max Z	vox	x	y	z
I > N							

	*Postcentral_Gyrus(L)	BA5	4.56	1068	-36	-38	64
	%Amygdala (L)	BA34	4.59	55	-24	-2	-20
I > C							
	Inferior_Parietal_Lobule(L)	BA40	4.19	307	-52	-48	50
	Middle_Temporal_Gyrus(L)	BA21	4.12	259	-64	-52	-2
	%Amygdala(L)	BA28	4.88	96	-18	-14	-14
	%Thalamus(Pulvinar)/(habenula)(L)	BA27	4.89	53	-16	-32	2

BA = Brodmann Area; Max Z = Maximum Z value within cluster; vox=number of voxels; x, y, z, coordinates in MNI space; All effects passed voxel-wise correction at p<.0025 after 10,000 permutations and also passed FWE cluster correction at p<.05 within the fronto-parietal and default mode network regions of interest except %, which were subcortical regions of interest with cluster extent of > 36 voxels; *also passes FWE with a whole-brain mask

The regions identified for the contrast of incongruent vs. neutral blocks yielded positive activation at the group level. Hence, higher levels of the Low Positive Affect-specific factor (i.e., less positive affect) were associated with a greater difference in activation between incongruent vs. neutral blocks. The main region identified was a large area that spans the post-central gyrus into superior parietal regions extending into BA 40 and BA 7 and which falls within the dorsal and ventral attention networks. Also identified for this contrast was a portion of the right thalamus as well as the left amygdala.

Similarly, all regions identified in the contrast of incongruent vs. congruent blocks also showed positive activation for the overall group contrast. Some of these effects, such as those observed for the inferior parietal lobe as well as activation in the left amygdala, were in regions overlapping those observed for the contrast of incongruent vs. neutral blocks.

In addition, there were some areas of activation in the incongruent vs. congruent contrast that appear to have a unique association with Low Positive Affect-specific factor that were not observed for the incongruent vs. neutral contrast. Cortically, these include portions of the middle temporal gyrus that is a portion of the fronto-parietal network and subcortically an area adjacent to the thalamus likely to be the habenula (Lawson, Drevets, & Rosier, 2013) as well as the amygdala.

In sum, levels of the Low Positive Affect-specific factor were associated with activation in posterior portions of the fronto-parietal network. Of note, a very strong association was observed with activation in emotion-related regions including the amygdala and a region that is likely the habenula.

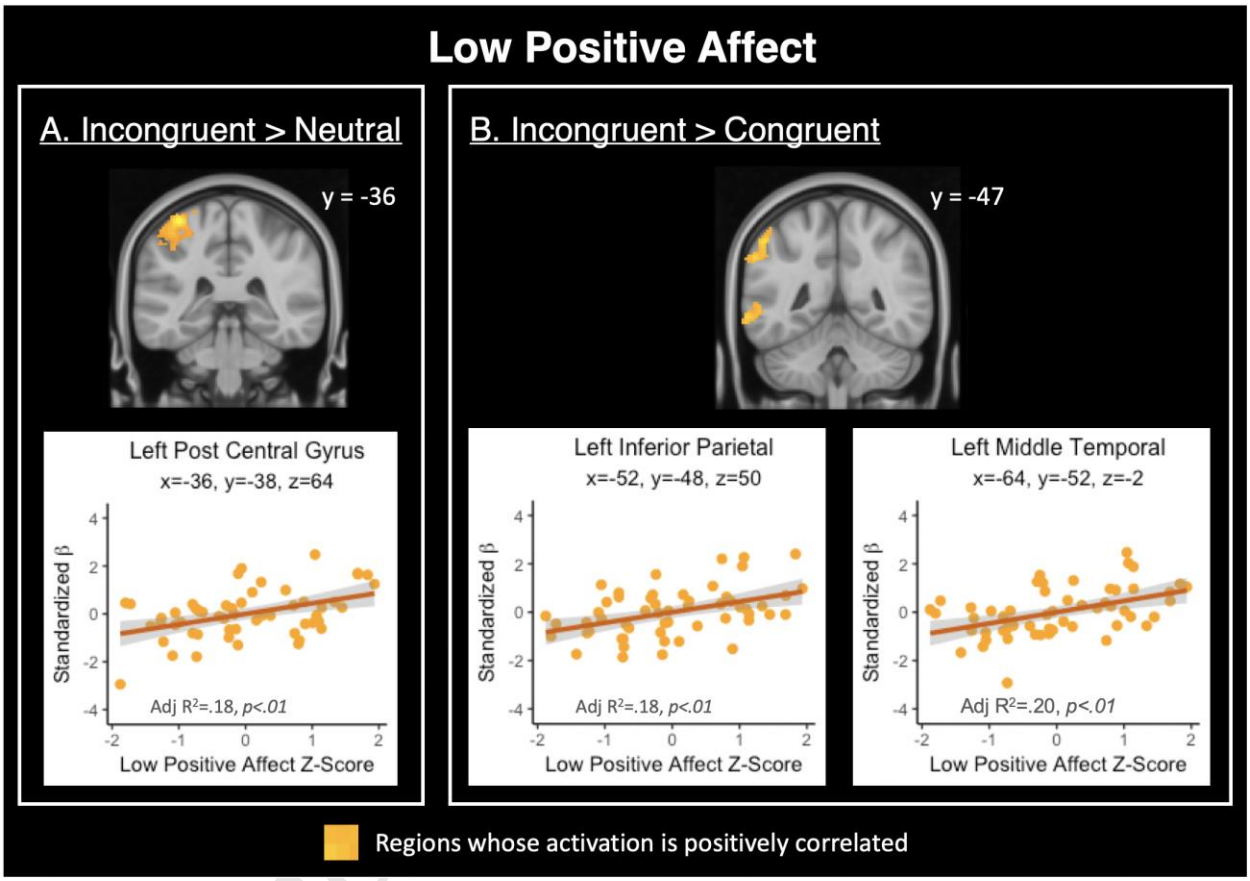


Figure 5. Brain regions whose activity is modulated by an individual's score on the Low Positive Affect-specific factor. Regions depicted passed permutation testing at a voxel-wise p<.0025 and FWE at p<.05 within the fronto-parietal and default mode network region of interest, except for left post-central gryus which passed FWE at whole-brain correction. All regions exhibited a positive association with the factor and are shown in red Scatterplots show the relationship between an individual's Z score on the factor score and the standardized beta for a given brain region for the relevant contrast. The standardized beta was calculated via fslmeants for a 9 mm diameter sphere centered at the relevant peak location listed in Table 6.

3.2.2.3. Anxious Arousal-specific Factor

There were only one associations between the Anxious Arousal-specific factor and patterns of brain activation, which was in a region of interest, the thalamus (see Table 6).

Table 6. Regions whose activation is significantly associated with level of the Anxious Arousal-specific Factor.

Contrast	Region	BA	Max Z	vox	x	y	z
I + C > N							
	%Thalamus	N/A	-5.44	40	6	-8	-2

BA = Brodmann Area; Max Z = Maximum Z value within cluster; vox=number of voxels; x, y, z, coordinates in MNI space; Effects passed voxel-wise correction at p<.0025 after 10,000 permutations and had a cluster extent of >36 voxels for subcortical regions of interest.

3.2.2.4. Anxious Apprehension-specific Factor

There were no associations observed with the degree of the Anxious Apprehension-specific factor after either of our two correction methods.

3.2.3. Effects related to Valence of the Task-Irrelevant Facial Expression – Main Effects

Across the entire group (regardless of level of symptoms related to a given dimension), we found one main region that was sensitive to the valence of the face, which is a portion of the medial frontal cortex that is located within the default model network (See Table 7). This effect was observed for incongruent trials for the contrast of positive (i.e., happy) > negative (i.e., angry) faces, which occurred because this region deactivates significantly more to negative than positive faces.

Table 7. Regions that show an overall group effect of emotional valence.

Contrast	Region	BA	Max Z	vox	x	y	z
Incongruent Positive Faces > Incongruent Negative Faces							
	Medial_Frontal_Gyrus(R)	BA10	4.35	469	4	48	12

BA = Brodmann Area; Max Z = Maximum Z value within cluster; vox=number of voxels; x, y, z, coordinates in MNI space; Effect passed voxel-wise correction at p<.0025 after 10,000 permutations and FWE at p<.05 within the fronto-parietal and default mode network regions of interest.

3.2.4. Effects related to Valence of the Task-Irrelevant Facial Expression - Covariate Results

The only factor that showed an effect related to the valence of the task-irrelevant facial expression was the Anxious Arousal-specific factor (see Table 8). More specifically, a small region of the left amygdala and the left thalamus, both regions of interest, shows non-significantly greater activation to negative (i.e., angry) than to positive (i.e., happy faces), indicating greater differentiation in response to the valence of the task-irrelevant face with increasing levels of the Anxious Arousal-specific factor. These results, however, should be interpreted very cautiously due to the small size of the clusters.

Table 8. Regions for which an effect of the valence of the face is associated with factors related to internalizing disorders

Contrast	Region	BA	Max Z	Vox	x	y	z
Anxious Arousal – specific factor							
Congruent Negative Faces > Congruent Positive Faces							
	%Amygdala(L)	N/A	4.24	12	-26	-8	-18
	%Thalamus(L)	N/A	4.29	13	-12	-28	6

BA = Brodmann Area; Max Z = Maximum Z value within cluster; vox=number of voxels; x, y, z, coordinates in MNI space; Voxel-wise correction at p<.0025 after 10,000 permutations; %, region of interest.

4. Discussion

The results of the current study provide insights into individual differences in emotional dimensions relevant to internalizing aspects of psychopathology, especially anxiety and depression, as they relate to regional patterns of brain activation when individuals are engaged in exerting cognitive control over affective stimuli. As an overview, findings revealed that higher scores on a Common Internalizing factor across symptoms of depression and anxiety are associated with differences in activity in both posterior and anterior portions of the medial cortex associated with the default mode network. In contrast, altered activity in parietal and temporal regions associated with the fronto-parietal and dorsal attention networks are more highly

associated with levels of the Low Positive Affect factor. Below we consider the associations of patterns of brain activation with each of these factors in turn.

4.1 Effects associated with the Common Internalizing factor

The most prominent finding was that levels of the Common Internalizing factor are associated with levels of activation that in regions of the default mode network, including portions of the superior frontal cortex, retrosplenial cortex and precuneus. In some ways, this finding is not surprising as the default mode network has been implicated in self-generated thought (Andrews-Hanna, Smallwood & Spreng, 2014), and a common pattern of cognitive processing in internalizing disorders involves repetitive negative thinking and/or self-focus. What is also notable is that these alterations are observed during a task requiring cognitive control, which at first glance might seem surprising. However, research suggests that activity in the cognitive control and default networks often shows reciprocal patterns of activation (Fox, Snyder, Vincent, Corbetta, Van Essen & Raichle, 2005), which make the alterations in default mode activity more comprehensible in the current context.

It is worth noting that prior studies have found that depression is associated with alterations in function of the default mode network (e.g., Kaiser et al., 2015). However, the current findings suggest that alterations in default mode functioning may be associated with common internalizing symptoms more generally. One possible way to reconcile these two findings is to consider that one of MASQ anhedonic depression subscales, Loss of Interest, fully loads on the Common Internalizing factor. As such, aspects of depression that overlap with common internalizing symptoms may be associated with alterations in the default mode network,

4.2 Effects associated with the Low Positive Affect – specific factor

Probably the most striking findings overall were observed for the Low Positive Affect-specific factor, which is associated with a variety of specific alterations in brain activity. Notably, it was the level of the Low Positive Affect-specific factor in particular, rather than levels of the Common Internalizing factor, that was associated with alteration in activation in posterior regions of the fronto-parietal control network and parietal portions of the dorsal attention network. This effect appears to be rather general, as it was observed both for the contrast of incongruent compared to neutral trials and for the more specific contrast of incongruent vs. congruent trials. This pattern suggests that the higher the levels of the Low Positive Affect-specific factor (i.e., less positive affect), the more these control regions are activated when there is incongruent emotional information in both the word and the face.

These findings help to clarify the association between depression and compromised executive processes (e.g., Snyder, 2013), suggesting that it may be low positive affect, rather than internalizing symptoms more generally, that is associated with altered cognitive control. As such, these findings are consistent with prior neuroimaging work suggesting that anhedonic depression is associated with alterations in functioning in posterior regions of DLPFC, most notably the inferior frontal junction (Herrington et al., 2010).

Also notable were a variety of effects in non-cortical regions of interest. Most notable were associations with patterns of activation in the amygdala, an effect not observed for the Common Internalizing factor. There were in addition, associations with activation in a region that is likely the habenula, which has been suggested to be involved in aversive processing, and which has been found to be hyperactive in depression (Lawson et al., 2017). Surprisingly, few alterations were found for regions related to reward-based processing, except for a small

subthreshold 13-voxel area of activation in the caudate (not listed). This absence may have occurred because our task does not involve reward, although it did involve valenced materials.

4.3 Effects associated with the Anxious Arousal-specific factor

In contrast to the findings discussed above, there were relatively few alterations associated with factors related to specific anxiety dimensions and none passed FWE. Yet levels of the Anxious Arousal-specific factor were associated with alterations in activity of the thalamus, a region of interest. In particular, increased levels on the Anxious Arousal-specific factor are associated with less of a differentiation in thalamic activity as a function of cognitive control demands. This anterior/midline portion of the thalamus has a high probability of connectivity (68%) to prefrontal regions according to the Oxford Thalamic Probability Atlas, is considered the "cognitive" rather than the sensory division of the thalamus (Saalman, 2014), is a region that is associated with resting-state connectivity to the salience network (Yuan, Di, Taylor, Gohel, Tsai et al., 2016), and in mice has recently been shown to determine reactions to visual threat (Salay, Ishiko, & Huberman, 2018).

In addition, increasing levels of the Anxious Arousal-specific factor were associated with increasing activation for angry as compared to happy faces in the amygdala. This pattern suggests increased sensitivity to potentially threatening information in individuals with higher levels on the Anxious Arousal-specific factor.

4.4 Effects associated with to the Anxious Apprehension-specific Factor

Somewhat surprisingly, no effects were observed for the Anxious-Apprehension specific factor, and the reasons for these null results is not clear. One possibility is that anxious apprehension tends to be a more cognitive factor with regards to emotional processing, associated with thoughts about impending or future events. As such, it may be that a focused

task, such as the cognitive control task used here, does not allow time for concurrent thoughts, and as such may mask any alterations in brain activation that could be observed. Arguing somewhat against this possibility is the fact that prior brain imaging studies that have measured anxious apprehension have revealed altered patterns of brain activation, most notably in left ventrolateral cortex (Engels et al., 2010). Those results, however, were obtained on a younger sample of emerging adults, and perhaps the relationship with regional brain activation changes with age.

4.5 Trends across dimensional factors

There is a trend worth noting regarding brain activation and levels across the different dimensional factors. In general, but not always, higher scores on a particular dimension were associated with less of a differentiation in activation between conditions that vary in cognitive control demand, such as the contrast between the incongruent condition in which there is higher demand due to the fact that the valence of the word and the face are conflicting (e.g., the word "happy" superimposed on an angry face) as compared to congruent trials in which no such conflict exits (e.g., the word "happy" superimposed on a happy face). This pattern suggests that individuals high in levels of dimensions related to internalizing psychopathology may exhibit less flexibility in their brain responses to cognitive control demands.

However, one structure that did not show such an effect was the amygdala, a central limbic system structure that has been implicated in the early processing of salient emotional information. Rather, the higher the level on the Low Positive Affect-specific factor (i.e., less positive affect), the greater the response in the amygdala for incongruent as compared to either congruent or neutral trials, that is, the more the amygdala becomes activated under conditions of

high control. It may be that emotional information that is conflicting in valence is more salient to individuals with higher levels of the Low Positive Affect-specific factor.

While activation of the amygdala varied with level of cognitive control with regard to the Low Positive Affect-specific factor, there was some weak evidence (due to limited cluster size) that its activation varied with the valence of the task-irrelevant face with regard to the Anxious Arousal-specific factors. With increasing levels of the Anxious Arousal-specific factor there is less of a difference in activation between happy and angry faces. This pattern seems to reflect an increased sensitivity to the negative (i.e., angry) faces, as at the group level individuals showed greater amygdala activation to happy than angry faces, which is consistent with prior reports of greater amygdala activation to task-irrelevant positive than negative words in an emotional Stroop task (Herrington et al., 2010).

We should also note that our findings were most robust for the left amygdala, and while activity was observed bilaterally in the right amygdala it was below our threshold for reporting. Recent work using MEG suggests that right amygdala responses to emotional faces are more transient and habituate more quickly than those in left amygdala, which are more sustained (Liu, Chen, Hsieh & Chen, 2015). It has been suggested that this pattern may indicate that right amygdala processing is more linked to autonomic arousal engendered by emotional faces while left amygdala is more involved in decoding or evaluating the significance of emotional faces.

4.6 Limitations and Future Directions

While the current study provides important insights, it is not without limitations. First, we used a conceptual model of anxiety and depression that organizes symptoms via a bifactor model with a common factor of internalizing symptoms and specific factors for low positive affect, anxious arousal and anxious apprehension. Presently this model is not commonly utilized across

the field as traditional DSM-based diagnostic categories and syndrome measures still predominate (Hankin et al., 2016). However, as described in the introduction, we argue that a bifactor model of internalizing psychopathology overcomes limitations of prior research, and similar models lacking the anxious apprehension dimension demonstrate construct validity in relation to symptom, affect, and dysfunction measures (e.g., Simms, Grös, Watson, & O'Hara, 2008; Simms, Prisciandaro, Krueger, & Goldberg, 2012). Moreover, we are currently validating the model in several large, independent samples, from adolescence to middle adulthood (Snyder et al., in preparation). In addition, because cognitive control deficits are not unique to internalizing disorders, a potential future direction would be to examine how more broad cross-diagnostic measures of psychopathology, such as the p factor (Caspi, Houts, Belsky, Goldman-Mellor, Harrington, Israel et al., 2014), might be related to the neural systems involved in cognitive control over emotional information.

Second, the current study used an unselected community sample to capture the full range of symptoms dimensionally in the general population. Results may differ in clinical or high-risk samples with higher levels of symptoms. For example, higher levels of anxious arousal and anxious apprehension symptoms may be associated with additional neural effects.

Third, our sample is restricted in age range and was limited to women. Nonetheless, while much work has been performed on emerging and young adults, and individuals age 60 and over, middle adulthood is a period of life that is often overlooked or ignored in research. This is a time of life when internalizing disorders remain highly prevalent (Kessler et al., 2005) so that understanding the brain systems underlying these disorders during this portion of the lifespan is important.

Fourth, our sample size was relatively small, and thus our results must be considered somewhat preliminary. Nonetheless, our task and our methods are conceptually driven and our analyses hypothesis-driven rather than purely exploratory.

Fifth, the results regarding subcortical structures should be viewed very cautiously as they were not corrected for multiple comparisons.

4.7 Summary

The current study provided evidence that unique patterns of brain activity during cognitive control tasks are associated with the common variance across internalizing disorders as well as with the more specific dimensions of low positive affect and anxious arousal. In particular, whereas common internalizing problems tended to affect activation in portions of the default mode network, specific aspects of low positive affect were more highly associated with changes in activation in portions of the fronto-parietal network, implicating them as potentially being important for the executive function deficits often observed in depression. Fewer associations were observed for specific dimensions of anxious arousal and none for anxious apprehension. The associations for anxious arousal-specific levels mainly involved activation of non-cortical regions, the thalamus and amygdala more specifically, consistent with arousal-related functions.

4.8 What is cognitive control without affect?

In terms of the theme of this special issue, the present results serve as a clear reminder that considering the neural mechanisms of cognitive control outside of the realm of affect likely provides only a restricted view on their function. While the results of the present study do not suggest that cognitive control depends specifically on affective processes, they do suggest that the way in which cognitive control is implemented likely depends on individual variation related

to affective processes. In particular, our results suggest that one's level of low positive affect can influence the degree to which parietal portions of the fronto-parietal and dorsal attention networks are engaged when cognitive control must be implemented. In addition, the results provide evidence of the specificity of that effect as such a relationship is not observed for the level of common internalizing symptomology more generally nor for symptomology related to anxiety (anxious arousal, anxious apprehension). Whether these factors might influence the activation of cognitive control regions in paradigms other than the Stroop task, of course, remains to be seen.

Another notable finding is the degree to which individual differences in the level of these factors influences patterns of activation in subcortical regions. Multiple patterns of association were found for portions of the thalamus and the amygdala. Such findings are a reminder of the degree to which bottom-up salience (as detected by the amygdala) or gating (as performed by the thalamus) of emotional material may influence the degree to which cognitive control is, or needs to be, exerted. In fact, recently it has been proposed that thalamic activation can help to enable rapid coordination between different cortical processors so as to aid in amplifying sensory information that is most task-relevant (Halassa & Kastner, 2017), a basic function required to exert cognitive control. Collectively these findings suggest that an increased emphasis in future studies on the connectivity and coordination between cortical systems involved in cognitive control (e.g., fronto-parietal, dorsal attention, ventral attention) and subcortical regions related to emotion and informational salience are likely to be warranted.

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Highlights

- Examined individual variation in factors related to internalizing psychopathology
- Influence on cognitive control in the face of emotional challenge was examined
- Common Internalizing factor levels were associated with default mode activation
- Low Positive Aspect-specific factor was associated with fronto-parietal activation
- Anxious Apprehension-specific factor was associated with thalamic activation