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Sex-specific neural activity when resolving cognitive interference in individuals with or without prior internalizing disorders

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ABSTRACT

The processing of cognitive interference is a self-regulatory capacity that is impaired in persons with internalizing disorders. This investigation was to assess sex differences in the neural correlates of cognitive interference in individuals with and without an illness history of an internalizing disorder. We compared functional magnetic resonance imaging blood-oxygenation-level-dependent responses in both males ($n=63$) and females ($n=80$) with and without this illness history during performance of the Simon task. Females deactivated superior frontal gyrus, inferior parietal lobe, and posterior cingulate cortex to a greater extent than males. Females with a prior history of internalizing disorder also deactivated these regions more compared to males with that history, and they additionally demonstrated greater activation of right inferior frontal gyrus. These group differences were represented in a significant sex-by-illness interaction in these regions. These deactivated regions compose a task-negative or default mode network, whereas the inferior frontal gyrus usually activates when performing an attention-demanding task and is a key component of a task-positive network. Our findings suggest that a prior history of internalizing disorders disproportionately influences functioning of the default mode network and is associated with an accompanying activation of the task-positive network in females during the resolution of cognitive interference.

1. Introduction

Internalizing disorders, including depression and anxiety, are characterized by a tendency to turn negative emotions inward when experiencing distress, as opposed to turning them outward, which is observed in externalizing disorders. The fact that females are at greater risk for internalizing disorders than males is well established (Eaton et al., 2012). Internalizing disorders, such as depression and anxiety, are highly comorbid and derive from common mechanisms, such as neuroticism (Hettema et al., 2006). Moreover, a large body of work examines the phenotypic presentation of internalized distress across development (Zahn-Waxler et al., 2000). Continuity between depression and anxiety, particularly among adolescent girls, has been observed (Costello et al., 2003); yet limited work examines sex differences in the neural underpinnings of internalizing illness.

We used a self-regulatory control task to examine whether sex-related differences may emerge among males and females who have a history of an internalizing disorder. Deficits in the self-regulatory control that is required to resolve cognitive interference have been

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implicated in the etiology of internalizing disorders, both in experimental (Austin et al., 2001; Joormann and Gotlib, 2008; Joormann et al., 2010) and neuroimaging (Berman et al., 2011; Pizzagalli, 2011) studies. To date few neuroimaging studies (Keller and Menon, 2009; Weissman-Fogel et al., 2010) have assessed sex differences in the functioning of neural circuits underlying cognitive or attentional processes. Such studies have the potential to explicate sex-specific mechanisms that may contribute to the documented higher prevalence of internalizing disorders among females (Angold and Worthman, 1993; Nolen-Hoeksema et al., 1999; Cyranowski et al., 2000; Kuehner, 2003). The current study assesses sex differences in the neural processing of cognitive interference and examines whether a previous history of an internalizing disorder is associated with different patterns of brain activations in males and females.

Self-regulatory control is required to resolve cognitive interference. Tasks such as the Stroop and Simon require activation of prefrontal regions to ignore a prepotent stimulus feature and respond in a task-relevant manner. Parallel, anti-correlated neural networks function in concert to support these self-regulatory processes. Fronto-striatal and fronto-parietal regions form a task-positive network that routinely increases in activity during task performance (Fox et al., 2005). Task-negative regions typically deactivate when individuals engage in goal-directed behavior (Shulman et al., 1997). These latter regions, including the posterior cingulate cortex (PCC), precuneus (PCu) (Uddin et al., 2009), inferior parietal lobe (IPL) and superior frontal gyrus (SFG), have collectively been labeled the Default Mode Network (DMN) (De Luca et al., 2006; Buckner et al., 2008). Relative deactivation of the DMN during a goal-directed task compared to baseline or a relatively easier condition is hypothesized to represent either greater activity while engaging in autobiographical or self-referential mind-wandering during the easier condition *or* greater active suppression of activity during an active or more challenging condition (i.e., responding to a condition requiring greater attention such as in the case of incongruent stimuli). Indeed, deactivation in medial parietal and medial frontal regions is hypothesized to reflect interruptions of internal introspection in the service of external attention-demanding tasks (Gusnard and Raichle, 2001; Hayden et al., 2009; Peterson et al., 2009; Peterson et al., 2014). Individuals with depression have demonstrated reduced cortical involvement in the resolution of interference when assessed with the Stroop task (Chechko et al., 2013), but sex differences during the resolution of cognitive interference, particularly as they relate to a history of internalizing disorders, have not been examined.

The current study is an exploratory examination of sex differences in brain activation during the performance of the Simon task in both the presence and absence of a history of an internalizing disorder. We examined internalizing disorders by examining both depression and anxiety diagnoses based on prior studies within the same cohort showing both illnesses to occur at elevated rates among high risk individuals and that an anxiety disorder often precedes the development of depression (Warner et al., 2008). Detecting significant sex-by-illness interactions would suggest that the effects of prior illness on brain systems that support the resolution of cognitive interference differ between females and males. We hypothesized that females would demonstrate longer reaction times than males and would deactivate DMN regions and activate task-positive regions to a greater extent than males during the resolution of cognitive interference; in addition, females with a history of an internalizing disorder would demonstrate the greatest deactivations.

2. Methods

We obtained functional MRI (fMRI) scans in 143 individuals, ages 7–54 years, who belonged to a 3-generation cohort followed through 5 waves of clinical assessments over more than 20 years, thereby ensuring an excellent, prospectively acquired knowledge of the psychiatric history of all participants. Diagnostic interviews across all waves (Weissman et al., 2005) were conducted using a semi-structured diagnostic instrument (the Schedule for Affective Disorders and Schizophrenia–Lifetime Version for adults, and a child version of the instrument that was modified for DSM-IV (American Psychological Association, 1994)) for participants 6–17 years of age (Mannuzza et al., 1986). The original project design was to follow offspring of the original Generation 1 cohort to examine high and low familial risk for Major Depressive Disorder (MDD). This study was initiated in 1982. Both the high and low risk groups were Generations 2 and 3 offspring of Generation 1. Generation 1 individuals were recruited from an outpatient clinic and were being treated for moderate to severe MDD with functional impairment and the offspring of these individuals formed the high risk group. In addition, the Generations 2 and 3 offspring of additional Generation 1 adults with no history of psychiatric illness recruited from the same community formed the low risk group. Wave 5 fMRI scans occurred between 2002 and 2007. This current sample consists of offspring (2nd and 3rd generation) of the original cohort who were consented to completing an fMRI scan. High and low risk was the original design of the study, but due to the low frequency of high risk females who did not develop illness, we specifically compare offspring with a previous diagnosis of Major Depressive Disorder or anxiety disorder, including Generalized Anxiety Disorder and Social Phobia and who were therefore categorized as previously "ill". Past history as well as current mental illness was assessed using the structured diagnostic interviews described above. Data from those with a history of illness were compared to those without a history of illness.

We assessed the main effects of sex in addition to sex-by-illness effects on brain activity. fMRI scan data were acquired from 143 individuals (40 children younger than 18, 103 adults). Scans were attempted but unsuccessful in 20 individuals. For technical reasons, fMRI scans were not attempted in another 8 individuals. Complete methods regarding this longitudinal study are described elsewhere (Weissman et al., 2005; Weissman et al., 2006; Peterson et al., 2014). The Children's Depression Rating Scale-Revised (CDRSR) for youth and the Hamilton Depression Rating Scale (HAM-D) for adults were converted into a *z*-score for each participant to index depression severity. The Revised Children's Manifest Anxiety Scale (RCMAS) and the Hamilton Anxiety Rating Scale (HAM-A) were also converted to a *z*-score to index anxiety severity.

2.1. Stimulus presentation

Visual stimuli were presented through MRI-compatible goggles (Resonance Technologies, Inc.). A series of white arrows pointing either left or right were displayed against a black background either to the left or right of a white gaze fixation cross-hair positioned at midline. The majority of stimuli were "congruent" arrows pointing in the same direction as their position on the screen (e.g. a rightward-pointing arrow presented to the right of midline). A smaller number of stimuli (~7%) were "incongruent", pointing in a direction opposite their position on the screen (e.g. a left-pointing arrow presented to the right of midline), spaced pseudorandomly every 13–16 congruent stimuli. Participants were instructed to respond as quickly as possible to the direction of the arrow by pressing a button on a response box. Stimulus duration was 1300 ms, with an inter-stimulus interval of 350 ms. Each run was composed of 102 stimuli (2.97 min duration), and each participant performed 10 runs. All stimuli were presented with E-Prime software 1.1 (Psychology Software Tools, Inc., Sharpsburg, PA 15215, USA) running on a Pentium-IV PC. A schematic of the Simon task is presented in Fig. 1.

2.2. Behavioral data analysis

Reaction times (RTs) and accuracy scores on each trial of the Simon task were entered as dependent variables in separate repeated measures, linear mixed models in SAS (SAS Institute Inc, Carey, NC) with risk group (high, low), illness (previously ill, healthy), stimulus congruence (incongruent, congruent), age, sex, and run number (0–10) included as independent variables. The effect of sex and prior illness on performance (RTs or accuracy) of congruent and incongruent trials was assessed by the statistical significance of the sex-by-illness interaction. We used an ANCOVA to assess differences across previously ill and healthy groups in interference scores, calculated as the difference in mean RTs during correct performance on the incongruent and congruent stimulus trials.

2.3. Image acquisition

Images were acquired on a Siemens Sonata 1.5 T scanner (Siemens AG, Munich, Germany) using a standard quadrature head coil. In all participants, a 3D spoiled gradient recall image was acquired for co-registration with the axial functional images and with the MNI (Montreal Neurological Institute) coordinate system. Functional images were acquired using a single shot gradient echo planar pulse sequence in groups of 16 axial slices per volume and 102 volumes per run. We acquired 10 runs for each participant. Parameters for the echoplanar images were TR = 1650 msec, TE = 30 ms, flip angle = 90°, acquisition matrix = 64 × 64,