Common and Dissociable Mechanisms of Executive System Dysfunction Across Psychiatric Disorders in Youth

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Abstract

Objective—Disruption of executive function is present in many neuropsychiatric disorders. However, determining the specificity of executive dysfunction within these disorders is challenging given high comorbidity of conditions. Here we investigated executive system deficits in association with dimensions of psychiatric symptoms in youth using a working memory paradigm, hypothesizing that common and dissociable patterns of dysfunction would be present.

Methods—We studied 1,129 youths who completed a fractal n-back task during fMRI at 3T as part of the Philadelphia Neurodevelopmental Cohort. Factor scores of clinical psychopathology were calculated using an itemwise confirmatory bifactor model, describing overall psychopathology as well as four orthogonal dimensions of symptoms including anxious-misery (mood / anxiety), behavioral disturbance (ADHD / conduct), psychosis-spectrum symptoms, and fear (phobias). The impact of psychopathology dimensions on behavioral performance and executive system recruitment (2-back > 0-back) were examined using both multivariate (matrix regression) and mass-univariate (linear regression) analyses.
Results—Overall psychopathology was associated with both abnormal multivariate patterns of activation and a failure to activate executive regions within the cingulo-opercular control network including the frontal pole, cingulate cortex, and anterior insula. Additionally, psychosis-spectrum symptoms were associated with hypo-activation of left dorsolateral prefrontal cortex, whereas behavioral symptoms were associated with hypo-activation of fronto-parietal cortex and cerebellum. In contrast, anxious-misery symptoms were associated with widespread hyper-activation of the executive network.

Conclusions—These findings provide novel evidence that common and dissociable deficits within the brain’s executive system are present in association with dimensions of psychopathology in youth.

INTRODUCTION

Deficits of executive function are present in a wide range of psychiatric disorders including attention deficit hyperactivity disorder (ADHD) (1), conduct disorder (2), and psychotic disorders such as schizophrenia (3,4). Executive deficits negatively impact everyday functioning (5), and contribute to diminished quality of life in many clinical populations (6,7). Consequences of executive deficits may be particularly acute in childhood and adolescence, and include increased interpersonal conflict, decreased academic achievement, and risk-taking behavior (7,8).

Many studies have investigated the neural basis of executive impairments in individual psychiatric disorders. Working memory is one of the most commonly studied components of executive function. For example, meta-analyses in patients with ADHD demonstrate hypoactivation within a network of regions including the dorsolateral prefrontal cortex, anterior cingulate cortex, thalamus, superior parietal lobule, and precuneus (9,10). Patients with schizophrenia also fail to recruit portions of the executive network including the dorsolateral prefrontal cortex (11–13). Likewise, conduct disorder is associated with a failure to activate a similar network of regions (14). Taken together, these studies suggest there are likely overlapping effects across disorders, with hypoactivation of the executive system being a common underlying brain phenotype. However, evidence exists for dissociable abnormalities among psychiatric disorders. For example, hyperactivation of executive regions have been reported in major depressive disorder and anxiety disorders (15–17). Nonetheless, some heterogeneity in results exists, and such hyperactivation has also frequently been reported in schizophrenia (18).

A case-control design in a single disorder is the predominant approach in the studies reviewed above, and thus most studies are unable to directly evaluate whether common executive deficits exist across disorders. Furthermore, while the incidence of psychiatric comorbidity is quite high, studies typically do not explicitly evaluate its impact. In epidemiological studies, approximately 40% of individuals meeting criteria for one diagnosis met criteria for at least one additional disorder in a different class (19). Thus, studies that use subjects with “pure” single diagnoses may not be representative. More recently, the neural basis of executive deficits across disorders have been investigated in an attempt to isolate regions of dysfunction specific to each diagnosis (20). However, studies
comparing multiple clinical groups are typically hampered by small sample size, and few prior studies compared more than two disorders at a time. Furthermore, as psychiatric symptomatology exists on a continuum of normal to abnormal, dimensional analyses that cut across categorical clinical diagnoses may both enhance power and improve biological interpretability (21). Thus, studies in large samples evaluating the impact of multiple dimensions of psychopathology on executive functioning are necessary.

Accordingly, here we used a dimensional approach to examine executive dysfunction with a working memory fMRI task in a sample of 1,129 youth imaged as part of the Philadelphia Neurodevelopmental Cohort (22,23). Notably, the ascertainment strategy used in the Philadelphia Neurodevelopmental Cohort differs substantially from studies using clinical help-seeking samples, instead employing a population-based approach that examines symptoms in non-help seeking youth. While such a design will likely have lower symptom severity than clinical samples, a population-based approach may nonetheless be valuable for investigating dimensions of psychopathology. We hypothesized that there would be both common and dissociable deficits in executive recruitment associated with different dimensions of psychopathology. Specifically, we predicted that general psychopathology would be associated with executive hypo-activation regardless of clinical diagnosis. Furthermore, we predicted that specific dimensions of psychopathology would be linked to dissociable regional patterns of impairment within the executive network.

METHODS

Participants

As previously described, the Philadelphia Neurodevelopmental Cohort is a collaboration between the Center for Applied Genomics at the Children’s Hospital of Philadelphia and the Brain Behavior Laboratory at the University of Pennsylvania (22,23). The current report considers the entire cross-sectional sample of 1,601 subjects imaged as part of the Philadelphia Neurodevelopmental Cohort; of these, 1,462 completed the n-back task described below. Following subject exclusions including medical co-morbidity, task non-performance, and image quality assurance (see Supplementary Methods), the final sample included in analyses was n=1,129 (mean age = 15.5 years; SD = 3.4 years; 520 males). This sample thus constitutes a super-set of subjects previously included in reports that focused on effects of working memory performance (24) and psychosis-spectrum symptoms (25).

Clinical assessment

As previously detailed (26,27), psychopathology symptoms were evaluated using a structured screening interview (GOASSESS). Computerized algorithms used endorsement of symptoms, their frequency and duration, and the presence of distress or impairment to determine whether DSM-IV criteria were met (see Supplementary Methods). The frequency and relevant demographic data for each screening diagnosis considered are detailed in Table 1. As in large-scale epidemiologic datasets (19), co-morbidity was quite common, with more subjects meeting criteria for more than one category (n=529) than a single category (n=249).
Psychopathology factor analysis

In order to parse this co-morbidity into orthogonal dimensions of psychopathology, we performed factor analyses of item-level data from GOASSESS. To produce stable factor scores, analyses utilized all subjects for whom clinical data were available (n=9,498) rather than only the subset who completed neuroimaging \(^2\). As initial exploratory factor analyses indicated correlated traits of psychopathology, we used a bifactor confirmatory model, which can produce orthogonal scores from correlated traits \(^2\).

Methods regarding estimation of the bifactor model will be presented in detail elsewhere (also see Supplementary Methods). Briefly, the confirmatory bifactor model (Figure 1A) was estimated using a Bayesian estimator in Mplus. As predicted by theory and supported by initial exploratory models, the four factors primarily represent anxious-misery (mood & anxiety) symptoms, psychosis-spectrum symptoms, behavioral symptoms (conduct and ADHD), and fear symptoms (phobias). Additionally, the bifactor model estimated a general psychopathology factor, representing the overall burden of psychopathology while controlling for the presence of specific symptom dimensions. Importantly, all five factors (including general psychopathology) from the bifactor model are orthogonal and can be considered jointly in analysis of imaging data. Factors scores within each of the categorical screening categories were as expected given item-level loading (Figure 1B).

Task paradigm, image acquisition and image processing

Task paradigm, image acquisition, and pre-processing methods were as previously reported \(^2\). Briefly, a fractal version of the n-back task \(^2\) was used to probe executive system function across three levels of working memory load (Figure 2A). The primary behavioral measure was \(d\)' a signal detection metric that limits the influence of response bias. Task performance \((d\)') across all levels of working memory load was related to categorical diagnosis from GOASSESS and dimensional factor scores using linear models while controlling for age and sex. Testing five dimensions of psychopathology were accounted for using Bonferroni correction.

fMRI, T1, and B0 images were acquired on the same scanner (Siemens 3T Tim Trio) for all subjects (see Supplementary Methods). Timeseries analysis of subject-level imaging data used FSL \(^2\) to model three condition blocks (0-back, 1-back, and 2-back); the primary contrast was 2-back > 0-back, which robustly recruits the executive network \(^2\). Subject-level statistical maps were distortion corrected, co-registered to the T1 image using boundary-based registration, and normalized to the MNI 152 1mm template using ANTs \(^2\) and then downsampled to 2mm. All transformations were concatenated so only one interpolation was performed.

Multivariate group-level analysis: Global associations with psychopathology

As a first step, we evaluated the degree to which dimensions of psychopathology from the factor analysis impacted overall multivariate patterns of activation (see Figure S1). To do this, we used multivariate distance-based matrix regression, a statistical technique developed originally for large-scale ecologic datasets that has recently been used in image analysis \(^2\); this was implemented using the vegan package in R \(^2\). Subject-level activation maps
are compared on a pairwise basis (Euclidean distance) to yield a distance matrix. Matrix regression is then used to test whether each phenotypic variable explains the distances among each participant’s activation patterns. In contrast to other multivariate methods, this approach allowed us to examine the influence of multiple dimensions of psychopathology simultaneously while also controlling for covariates (age, sex, and in-scanner motion). Multiple tests were accounted for using Bonferroni correction as above.

**Mass-univariate group-level analysis: Regional associations with psychopathology**

While the multivariate analysis detailed above provided an estimate of the degree to which dimensions of psychopathology impacted the global pattern of activation, this analysis does not evaluate regional effects. Accordingly, we next conducted a standard mass-univariate analysis using a general linear model implemented in FSL (30). We evaluated the effect of each dimension of psychopathology within this linear model, with covariates as above. Additionally, we investigated whether dimensions of psychopathology that showed a significant effect were significantly different from each other using an F-test across dimensions. Type I error control was provided by cluster correction using 10,000 Monte-Carlo simulations (voxel height of $z > 3.09$; cluster probability of $p < 0.001$; minimum cluster size of $k=67$) (34). All analyses described below used unmasked, whole-brain voxelwise data. Images were displayed using Caret.

**Supplementary analyses**

In order to evaluate whether potentially confounding factors influenced observed results, we conducted a series of supplementary analyses. This included a) removing the minority (11.4%) of subjects who were taking psychoactive medication; b) including task performance ($d'$) as a covariate; c) excluding subjects with poor performance (>7 non-responses) on the 2-back condition; and d) including mean accuracy on an out-of-scanner computerized neuropsychological battery, race, assessment-scan interval, maternal education, and in-scanner performance ($d'$) together as covariates in one model.

**RESULTS**

**Multiple dimensions of psychopathology impact task performance**

As expected, increasing working memory load was associated with fewer correct responses to targets and increased false positive responses to foils (Figure 2B & C). These measures were integrated using the signal detection measure $d'$. As expected, $d'$ varied considerably by screening categorical diagnosis (see Table 1). When summarized as psychopathology dimensions, several factors significantly impacted working memory task performance (Figure 2D). Higher levels of both overall psychopathology ($t_{1124}=2.58$, $p=0.001$) and behavioral symptoms ($t_{1124}=3.82$, $p=0.0001$) were associated with lower working memory performance. In contrast, higher levels of anxious-misery symptoms were associated with a trend towards better working memory performance ($t_{1124}=2.45$, $p=0.015$). There was not a significant relationship between fear or psychosis and working memory performance.
Overall psychopathology alters global patterns of executive system recruitment

As expected, the 2-back > 0-back contrast robustly recruited the entire executive network, and resulted in de-activation of non-executive regions (Figure 2E). We next evaluated whether dimensional psychopathology was associated with changes in this multivariate pattern of activation and de-activation using multivariate distance-based matrix regression. This procedure revealed that overall psychopathology was associated with a significant disturbance in the global pattern of executive system recruitment (p=0.009). Other symptom dimensions did not have a significant relationship; non-significant trends were observed for behavioral (p=0.044) and anxious-misery (p=0.092) symptoms.

Dimensions of psychopathology differentially impact regional executive activation

Multivariate distance-based matrix regression evaluates the presence of global multivariate effects, but is not sensitive to regional changes. Accordingly, we used mass-univariate generalized linear models to examine the relationship between dimensions of psychopathology and executive system activation (Figure 3, Table S1). As suggested by multivariate results, overall psychopathology had the most robust impact on executive activation. Higher levels of overall psychopathology were associated with diminished activation of bilateral frontal pole, anterior cingulate cortex, anterior insula, thalamus, and precuneus. Behavioral symptoms were associated with diminished activation of frontoparietal cortex as well as thalamus and cerebellum. Psychosis-spectrum symptoms were associated with diminished activation of the left dorsolateral prefrontal cortex. Fear (phobia symptoms) was associated with diminished activation of a marginally significant cluster of medial frontal cortex, but this effect did not survive supplementary analyses (see below) and was not evaluated further. Finally, in contrast to the hypo-activation described above, anxious-misery symptoms were associated with a marked hyper-activation of multiple executive regions including anterior cingulate cortex, dorsolateral prefrontal cortex, parietal cortex, and thalamus. Notably, a small area of overlapping significant effects across dimensions was seen in the left dorsolateral prefrontal cortex (MNI coordinates: x=−28, y=−6, z=58; k=10). Significant differential effects of each dimension were present in multiple executive regions (Figure 4, Table S2). This was driven by the divergent impact of global psychopathology (hypo-activation) and anxious misery (hyper-activation). We did not find any differences in default mode regions where task-induced deactivation was present.

Supplementary analyses

Overall, convergent results were obtained from supplementary analyses where participants taking psychoactive medications were excluded (Table S3), when working memory performance was included as a covariate (Table S4), and when multiple additional covariates were included (Table S5). When participants with poor performance on the 2-back condition were excluded, psychosis-spectrum symptoms were associated with a marginally significant cluster of hyperactivation in the cingulate gyrus; otherwise results were similar (Table S6). As noted above, fear did not have a significant association with activation in any of the supplementary analyses.
DISCUSSION

In this large study of psychopathology in youth, we examined associations between diverse psychopathology and activation of the brain’s executive system during a working memory task. To account for the fact that psychiatric disorders are highly co-morbid, factor analysis of the psychopathology data using a bifactor model allowed us to examine both general psychopathology and orthogonal dimensions of psychopathology. Overall psychopathology was associated with a significant alteration of the global multivariate pattern of activation. Furthermore, dimensions of psychopathology significantly influenced regional patterns of activation in different ways. In contrast to the hypo-activation seen in association with overall psychopathology, anxious misery symptoms were associated with hyper-activation of the same network. Taken together, these data emphasize that dimensions of psychiatric symptomatology are associated with both common and distinct deficits within the executive system.

Evidence for common executive deficits across psychiatric syndromes in youth

The most robust finding in the present study is evidence of common executive deficits attributable to overall psychopathology present across categorical clinical diagnoses. This was observed on both a global and local scale: overall psychopathology was associated with an alteration of the global multivariate pattern of activation, driven by regional hypoactivation in a network of executive regions including the frontal pole, anterior cingulate, anterior insula, and precuneus. These results accord with a copious literature of case-control studies from multiple individual disorders, and moreover highlight the centrality of executive dysfunction across major psychiatric syndromes.

We were able to estimate the influence of overall psychopathology across disorders through the use of a bifactor analysis of the item-level responses from the psychopathology screening interview. This approach obviates several major obstacles to estimating common deficits across traditional categorical diagnoses. First, when co-morbidity is represented in standard models as shared variance, it is controlled for but cannot be estimated. Estimating overall psychopathology may be particularly important in youth where the pattern of psychopathology may not fit standard diagnostic criteria in context of ongoing development. Second, strongly non-random patterns of comorbidity exist between different disorders (19). For example, mood and anxiety disorders have a high rate of comorbidity, as do ADHD and conduct disorders. Third, the frequency of each diagnosis varies considerably; thus the statistical power to estimate the impact of each individual diagnosis is not equal. Fourth, categorical diagnoses are by definition dichotomous, and important dimensional effects cannot be examined.

Crucially, each of these problems can be overcome through modeling of latent dimensions of psychopathology. Here we used confirmatory factor analysis to estimate a bifactor model, which provides orthogonal scores for every subject in each psychopathology domain, as well as a score for general psychopathology. These orthogonal scores can thus be included in a single model that can estimate dissociable dimensions of psychopathology with equal power, as well as the impact of overall psychopathology through the general score. The regions implicated by overall psychopathology include the frontal pole, anterior cingulate cortex,
and anterior insula. Notably, all these regions are part of the cingulo-opercular control network (also called the salience or ventral attention network), which is consistently identified as among the most reproducible large-scale functional brain networks both at rest and during task performance (35). This network is critical for cognitive control, and is particularly implicated in maintenance of task sets and error monitoring (36). These regions are among the most commonly impaired in case-control studies of schizophrenia, ADHD, and conduct disorder, suggesting that dysfunction of this network is not associated with one specific domain of psychopathology (4,10,37). Further support is provided from a large-scale meta-analysis by Goodkind et al., who found that gray matter loss in these cingulo-opercular regions was present across psychiatric disorders and associated with impaired executive function (38).

**Orthogonal dimensions of psychopathology are associated with dissociable deficits**

In addition to robust effects of overall psychopathology, we also identified both regionally and directionally dissociable effects of specific dimensions of psychopathology. Behavioral symptoms were associated with diminished activation of a network of regions including fronto-parietal cortex, thalamus, and cerebellum, whereas psychosis-spectrum symptoms were associated with hypo-activation of the left dorsolateral prefrontal cortex. The behavioral dimension loaded most prominently onto items assessing externalizing disorders such as ADHD, conduct disorder, and oppositional defiant disorder. Results are consistent with case-control studies in each of these disorders, which have demonstrated hypo-function of executive regions including most commonly fronto-parietal regions (10,20). Similarly, dysfunction of the dorsolateral prefrontal cortex is considered one of the cardinal impairments of psychosis (39). However, it should be noted that the effects of the psychosis spectrum observed here are more circumscribed than those typically reported; this may be due to the use of a population rather than a clinical sampling strategy, a focus on sub-threshold psychosis symptoms, and accounting for overall psychopathology through the bifactor model. However, consistent with the current results, in our previous report on psychosis-spectrum symptoms in this sample we observed that hypo-activation of executive regions was linked to cognitive performance but not to severity of positive psychotic symptoms, suggesting a substantial effect of overall impairment rather than psychosis per se (25).

In contrast to the diminished recruitment seen in other symptom domains, anxious-misery symptoms were associated with widespread hyper-activation of the executive network. Indeed, after accounting for overall psychopathology, anxious-misery symptoms were associated with a trend towards better working memory performance. However, executive hyper-activation is unlikely to be simply an epiphenomenon associated with working memory performance, as hyper-activation was still seen in sensitivity analyses that controlled for both in-scanner and out-of-scanner cognitive performance. This result is consistent with several studies of executive function in major depression and anxiety disorders that have found over-activation of executive regions (15–17). In contrast to the deficient ability to recruit the executive network seen in association with other symptom dimensions, these data suggest that mood and anxiety symptoms are associated with an inefficient executive system, where higher levels of executive network activation occur. It
should be noted that participants in our sample who screened positive for mood and anxiety disorders frequently also had high levels of overall psychopathology. As these dimensions have directionally opposite associations with executive recruitment, the relative presence of co-morbidity in a given sample could conceivably result in divergent results.

Limitations

Certain limitations of the present work should be noted. First, the young community-based sample studied here had diminished symptom severity compared to that found in typically older help-seeking samples drawn from clinical practices. Drawing from a different distribution of symptoms may result in reduced generalizability to clinical populations. However, the approach used here allowed us to accrue a larger, mainly unmedicated sample at a single site and scanner, and is well suited to investigating broad dimensions of psychopathology. A second important limitation is that this cross-sectional report does not include longitudinal data. As our prior work in this dataset has demonstrated that between-subject cross-sectional age effects are relatively subtle (24), within-subject longitudinal data will be particularly informative regarding whether specific symptom domains are associated with development of executive deficits over time. Third, certain important classes of psychopathology such as substance use that have been shown to impact executive function were not considered in the current analysis (40). Fourth, despite prior research showing abnormalities of the default mode network in multiple psychiatric disorders, we did not find significant effects in the default mode network; this may be due to the task paradigm employed. Finally, as previously noted (26,27), the highly-structured screening format of GOASSESS may have resulted in high sensitivity but relatively diminished specificity, leading to over-estimation of the frequency of several disorders. Alternatively, high rates of endorsed symptoms may accurately reflect this particular sample. Although factor-analytic results of the GOASSESS appear consistent with prior findings and lend support to the validity of the measure, ongoing longitudinal follow-up with semi-structured assessments applying DSM disorder criteria will allow further evaluation of the clinical relevance and stability of the current findings.

Conclusions

These data provide novel evidence regarding common and dissociable executive system deficits across multiple dimensions of psychopathology in young people. Results emphasize that executive dysfunction is present in association with overall psychopathology across traditional categorical psychiatric diagnoses, underscoring this system’s central relevance for circuit-based conceptualizations of neuropsychiatric disorders such as the NIMH Research Domain Criteria (RDoC) (21). These results may suggest that interventions seeking to enhance executive function may not fit well within the existing categorical diagnostic framework, and may be beneficial to individuals across diverse clinical syndromes where executive deficits are present. Future research employing longitudinal designs may motivate targeted early interventions that seek to mitigate executive dysfunction in youth before negative outcomes accrue.
Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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REFERENCES


Figure 1. Bifactor model of common and divergent dimensions of psychopathology across categorical screening diagnoses

The input data to the bifactor model were 112 items from the GOASSESS screening diagnostic interview, resulting in orthogonal dimensions of psychopathology (A). Mean (SD) factor scores of each dimension for each screening diagnosis (with at least n=20) is displayed in (B).
Figure 2. Working memory task paradigm, behavioral performance and contrast of interest

A fractal version of the n-back task was used to probe working memory function where working memory load was varied parametrically across three levels (A). Higher working memory load was associated with fewer correct responses to targets (B) and more false positive responses to foils (C). Correct responses and false positives were summarized across all levels of working memory load using the signal detection metric $d'$ to provide an integrated measure of working memory performance. Task performance was reduced in association with both overall psychopathology and behavioral symptoms; anxious-misery.
was conversely associated with a trend towards improved task performance (D). The contrast of interest (2-back > 0-back) robustly activated the entire executive system and de-activated non-executive regions (E).
The association of each dimension of psychopathology with executive network activation (2-back > 0-back) was examined using linear regression. The most robust effects were seen for overall psychopathology, where greater symptom severity was associated with diminished activation of the frontal pole, anterior cingulate, anterior insula, thalamus, and precuneus. Behavioral symptoms were associated with fronto-parietal, thalamic, and cerebellar hypoactivation; psychosis-spectrum symptoms were associated with diminished activation of the left dorsolateral prefrontal cortex. In contrast to the observed hypo-activation for all
other dimensions of psychopathology, anxious misery was associated with hyper-activation of regions within the executive network, including the dorsolateral prefrontal cortex and anterior cingulate cortex. All analyses included age, sex, and in-scanner motion as covariates; images thresholded at z>3.09, corrected p<0.001. Scatter plots were drawn from significant clusters identified by red circles. Activation is plotted in arbitrary BOLD units. For detailed results see Tables S1.
Figure 4. Differential effects of psychopathology on executive system activation
A linear model comparing the differential impact of each dimension of psychopathology revealed significant differences in multiple executive regions including the anterior cingulate cortex, frontal pole, and dorsolateral prefrontal cortex. Differential effects were driven by the divergent impact of anxious misery (hyper-activation) and overall psychopathology (hypo-activation). Activation is plotted in arbitrary BOLD units. Shaded area represents 95% confidence intervals. For detailed results see Table S2.
### Table 1
Demographic information by screening diagnostic category

Individual subjects may be present in multiple categories due to co-morbidity.

<table>
<thead>
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<th>Category</th>
<th>n</th>
<th>Mean Age (years)</th>
<th>S.D. Age (years)</th>
<th>Female (%)</th>
<th>Caucasian (%)</th>
<th>Mean Maternal Education (years)</th>
<th>S.D Maternal Education (years)</th>
<th>Mean N-back Performance ($d'$)</th>
<th>S.D N-back Performance ($d'$)</th>
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