The Central Executive Network in Schizophrenia: A Meta-Analysis of Structural and Functional MRI

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Introduction

- The neural architecture of executive functions (EF) are of considerable interest given the clinical utility of EF as transdiagnostic predictors of adaptive functioning.
- The central executive network (CEN) is a functional brain network with central hubs in the prefrontal cortex and posterior parietal cortex, important for goal-directed behavior and associated with cognitive processes such as attention and working memory.
- Meta-analyses (Yuan & Raz, 2014) have shown a consistent positive relationship between prefrontal cortex (PFC) and EF task performance in healthy adults, with increases in measures of cortical integrity (i.e. volume or thickness) associated with better EF performance.
- There is a gap in the meta-analytic literature regarding the relationship of EF as a predictor of neurocognitive functioning, the concordance between structural and functional architecture, and the relationship with neuropsychological assessments of EF.
- The core EF deficits and neural abnormalities consistently observed in individuals with Schizophrenia (SCZ) provide an important population to study the relationship of EF, neuropsychological testing, and the structure and function of the CEN.

Research Questions

- Is there a positive association between increased functional blood oxygen level dependent (BOLD) activity and better performance on EF tasks in individuals with schizophrenia?
- Is there a positive association between increased cortical volume and thickness and better performance on EF tasks in individuals with schizophrenia?
- Is there concordance between the functional and structural MRI measures of EF in individuals with schizophrenia?

Method: Literature Search, Article Exclusion & Registration

Literature Search

Two separate literature searches of PubMed and EBSCO (including PsycINFO and PsycARTICLES) conducted in May 2019 included the following terms:

- **Structural**: (dorsolateral OR dorsal lateral OR BA9 OR BA46 OR BA8 OR BA10 OR posterior parietal OR parietal lobule OR BA5 OR BA7 OR BA49 OR BA30) AND (volume* OR atrophy OR cortical thickness OR cortical thinning OR morphometry) AND (executive OR card sort* OR color word OR Stroop OR trail* OR verbal fluency OR working memory) AND (schizophren* OR psychosis)
- **Functional**: (central executive OR frontal executive OR frontal parietal) AND (functional MRI OR fMRI OR functional connectivity OR BOLD) AND (executive OR card sort* OR color word OR Stroop OR trail* OR verbal fluency OR working Memory) AND (Schizophren* OR Psychosis)

Exclusion Criteria

- Case Studies
- Research of non-human subjects
- Human participants under 18 years of age

Inclusion Criteria

- 1+ structural neuroimaging measure of
  - grey matter volume, thickness, or morphometry in regions of interest OR
  - Functional neuroimaging of either task or resting state BOLD fluctuations
- 1+ measure of EF
- Statistics delineating the relationship between EF and imaging

Protocol Registration

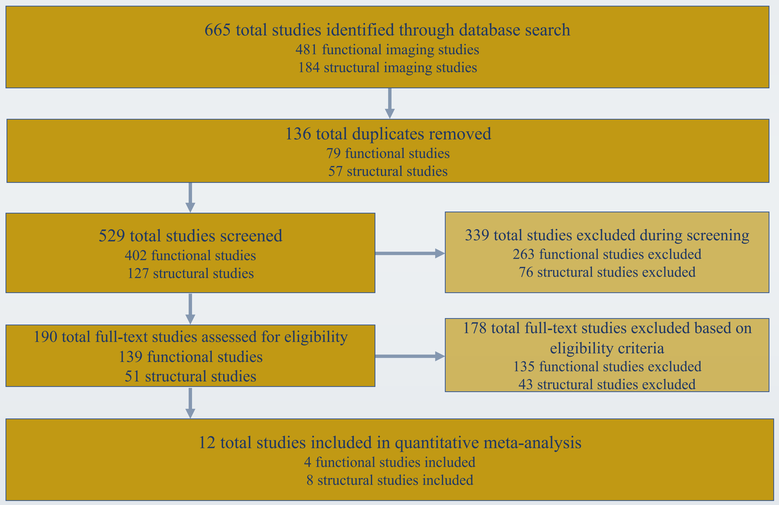
- Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines were followed in the creation of the protocol for this study (Moher, Liberati, Tetzlaf, Altman, The PRISMA Group, 2009)
- The protocol for this study is registered under the National Institute for Health Research (NIHR) PROSPERO International prospective register of systematic reviews (ID: CRD42019142764)

Method: Data Coding and Extraction

Data Extraction

- Trained graduate research assistants extracted the following variables:
  - Year Published
  - Sample Size
  - Mean Age
  - Age Range
  - Standard Deviation of Age
  - % Female
  - % Left-Handed
  - Country of Origin
  - EF Task
  - Statistic Coefficient between Imaging and EF Performance
  - Brain Region
- EF tasks were coded as one of the following:
  - Stroop/Color Word (CWI)
  - Verbal Fluency (VF)
  - Working Memory (WM)
  - Trail Making Test (TMT)
  - Wisconsin Card Sorting Task (WCST)
  - EF Composite Score (EFC)
- Studies with multiple EF tasks or multiple brain regions were collapsed under a single effect size by using Fischer's Z transformation (*Zr*) of correlation coefficients, averaging *Zr*, and converting the average back to correlation coefficients for initial analyses.

Study Eligibility Flow Diagram



Flow diagram adapted from Moher et al., 2009

Method: Effect Size Calculations & Statistical Modeling

Effect Size Calculations

- Meta-Essentials workbook for partial correlation (Suurmond, van Rhee, & Hak, 2017; Van Rhee, Suurmond, Hak, 2015) data was utilized to conduct random effects modeling in this study.
- Fisher's transformation, *Zr,* was used for each correlation coefficient to determine the effect size for each sample.

Statistical Modeling

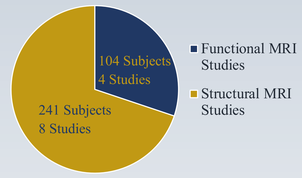
- Between-study variance and subject-sampling variance estimate was used to compute new weights for random-effects analyses.
- Mean effect sizes were computed for groups by weighting each effect size by its sample size.
- 95% confidence intervals (CI) were calculated using standard errors for each group of studies.
- Mean effect sizes for each group were generated from random effects modelling.
- Significance of between groups differences were compared using analysis of variance statistical analysis and determining if CIs overlapped.

Results

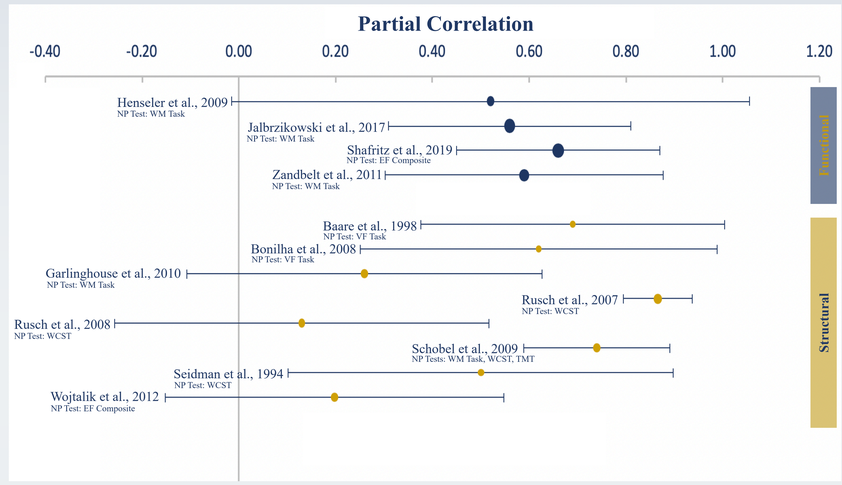
Sample Characteristics

	Age (*M* years)	Female (%)
Functional MRI Studies	27.56	25.0%
Structural MRI Studies	33.01	32.5%

Population Samples



Functional and Structural Imaging Sample Effect Sizes and 95% CIs



Statistics

- The strength of the brain behavior relationship pooled across both modalities was large (r=0.59).
- Larger size in structural volumes is associated with better performance on measures of EF (r=.57, 95% CI=.26-.75).
- Greater BOLD activation is associated with better performance on measures of EF (r=.59, 95% CI= .49-.65).

Conclusions & Discussion

- This study reveals concordance in the brain behavior relationship between functional and structural imaging modalities, such that larger size and greater BOLD activation were both associated with better performance on measures of EF in individuals with schizophrenia.
- On a meta-analytic level, when assessing the relationship between brain and EF behavioral performance, both structural and functional imaging are similarly predictive of EF performance when taken in hubs of the CEN.
- The strength of the brain behavior relationship in schizophrenia found in our study (r=0.57) is comparatively stronger than that found in healthy adults (r=.08-.23) in a previous meta-analysis (Yuan & Raz, 2014).
- Findings of this study are impactful in the context of methodological decisions in multi-modal neuroimaging research.
- Because traditional neuropsychological measures of EF were validated in lesion studies, future research should explore the relationship between brain structure and volume and EF performance between healthy and neuropsychiatric groups.

References

Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). *P*referred *R*eporting *I*tems for *S*ystematic Reviews and *M*eta-*A*nalyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

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