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Neural responses to incongruency in a blocked-trial Stroop fMRI task in major depressive disorder

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Abstract

Background—Patients with major depressive disorder (MDD) perform poorly on the Stroop task, which is a measure of the executive control of attention, with impaired interference resolution. The neural correlates of this deficit are not well described. To examine how this deficit relates to pathophysiological abnormalities in MDD, we conducted an fMRI Stroop study comparing MDD subjects to controls.

Methods—Forty-two unmedicated patients with current MDD and 17 control subjects underwent fMRI scanning with a color-word Stroop task. Subjects assessed font color during alternating color identification (ex. ‘XXXX’ in blue) and incongruent color/word blocks (ex. the word ‘red’ in blue). We examined neural activation that was greater in incongruent than color identification blocks ($Z > 2.3$ and corrected $p < 0.05$), controlling for trial-by-trial reaction time.

Results—Compared to controls, MDD subjects exhibited lower activation during incongruent blocks across multiple brain regions, including middle frontal gyrus, paracingulate and posterior

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Contributors

J.G.K. conceived and designed this study with guidance from J.J.M.. T.K., J.M.M. and N.S. contributed to analysis and T.K., J.M.M. and J.G.K. interpreted the data. M.A.O. supervised diagnostic assessments. J.M.M., J.K., and R.V.P. supervised fMRI acquisition. All contributed to drafting the article and final approval.

Conflict of interest

Dr. Kikuchi has received manuscript fees or speaker’s honoraria from Astellas Pharma, Dainippon Sumitomo Pharma, GlaxoSmithKline, Jansen Pharmaceutical, Kyowa Hakko Kirin, Otsuka Pharmaceutical, Pfizer, Shionogi and Yoshitomiya within the past 5 years. All are unrelated to this article. Dr. Miller has received financial compensation for psychiatric evaluations of subjects enrolled in medication studies sponsored by Pfizer and Orexigen Therapeutics unrelated to this article. Dr. Oquendo received financial compensation from Pfizer for the safety evaluation of a clinical facility, unrelated to the current manuscript, and was the recipient of a grant from Eli Lilly to support a year of the salary for the Lilly Suicide Scholar, Enrique Baca-Garcia, MD, PhD. She has received unrestricted educational grants and/or lecture fees from Astra-Zeneca, Bristol Myers Squibb, Eli Lilly, Janssen, Otsuka, Pfizer, Sanofi-Aventis, and Shire. Her family owns stock in Bristol Myers Squibb. Dr. Mann received past grants from Novartis and GSK. Dr. Parsey, Mr. Schneck and Dr. Keilp have nothing to disclose.

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cingulate, precuneus, occipital regions, and brain stem. No brain regions were identified in which MDD subjects were more active than controls during incongruent blocks.

Limitations—Not all MDD subjects were antidepressant-naïve.

Conclusions—Brain regions related to executive function, visual processing, and semantic processing are less active during processing of incongruent stimuli in MDD subjects as compared to controls. Deficits of attention in MDD may be the product of a failure to maintain activity across a distributed network in a sustained manner, as is required over the sequential trials in this block design. Further studies may clarify whether the abnormalities represent a trait or state deficit.

Keywords

Stroop task; functional magnetic resonance imaging; depression; executive function; incongruency; attention

Introduction

Studies of neuropsychological function in major depressive disorder (MDD) have identified an array of cognitive disturbances associated with this illness, including impairments of attention, working memory and executive function (Murrough et al., 2011; Veiel, 1997; Zakzanis et al., 1998). The Stroop task (MacLeod, 1991; MacLeod and Sheehan, 2003) is a measure of the executive control of attention that is among those tests commonly affected by depression. In an early meta-analysis (Zakzanis et al., 1998), they found an effect size of approximately 0.63 for poorer interference resolution on this task in MDD; comparable effect sizes were found in our own more recent work (Keilp et al., 2008). Interference resolution during the Stroop task is likely to affect adaptive cognitive performance in everyday life; is possibly related to the risk for suicidal behavior (Keilp et al., 2008; Keilp et al., 2001; Legris et al., 2012); and is predictive of poor antidepressant treatment outcome in depressed elderly (Sneed et al., 2007).

The Stroop task is one of the most extensively studied cognitive paradigms in functional imaging studies (Leung et al., 2000; Mead et al., 2002; Nee et al., 2007; Peterson et al., 1999; Roberts and Hall, 2008; Roelofs and Hagoort, 2002). These studies have identified brain activity during Stroop task performance across multiple brain regions, especially anterior cingulate cortex, lateral prefrontal cortex, lingual gyrus, extrastriate cortex, and perisylvian language areas. Use of the Stroop task in functional imaging studies of individuals with depression may shed light on alterations in the attention network that are related to major depression.

There have been few studies to date comparing brain activity during Stroop task performance between MDD subjects and controls. One study examining adults with MDD showed higher activity relative to controls in rostral anterior cingulate gyrus and left dorsolateral prefrontal cortex during interference trials of a Stroop task using an event-related, mixed trial design (Wagner et al., 2006). The Stroop task in that study was atypical in that response options were presented in a multiple-choice format, with two possible response options on the left and right of the screen, below the target stimulus, in an effort to reduce the need to memorize key presses using a manual response. A second study of adolescents found severity of depression correlated positively with activity in left dorsolateral prefrontal cortex and anterior cingulate gyrus – consistent with findings in MDD patients in the Wagner et al study – and negatively with activity in right dorsolateral prefrontal cortex during Stroop task performance (Killgore et al., 2007). Stroop stimuli in that study were presented in a blocked fashion, in separate runs, with a verbal response.

Our own behavioral work suggests that in a blocked format, individuals with MDD will perform relatively more slowly in interference blocks compared to non-interference blocks (Keilp et al., 2008). It is unknown if activity in task-relevant brain regions such as anterior cingulate gyrus or dorsolateral prefrontal cortex will remain elevated throughout the block, as was found for individual trials in event related designs such as that employed by Wagner and colleagues (Wagner et al., 2006), or whether activation will differ in other ways. In the study reported here, we examined brain function during a blocked task that was a translation of the computerized behavioral task that we had previously administered. Based on the classical Stroop paradigm (MacLeod, 1991), this task compared blocks of colored X's to blocks of incongruently-colored color names. While this type of design does not allow direct comparison of congruent vs. incongruent stimuli, it is comparable to the version of the task that we have used in our clinical studies. More importantly, it avoids the tendency of subjects to exploit the blocking of stimuli. Since stimuli are blocked, subjects are aware that a set number of stimuli will be similar. The use in other task designs of congruently colored words in a block allows subjects to switch from identifying the color of these items (a harder task) to simply reading the word (an easier task). This defeats the goal of the procedure to compare color identification in conditions where there is no interference, and where there is interference. The use of colored X's in the non-interference block of the current task ensures that subjects will adhere to the instructions to identify the color of the stimulus, because it removes any potential "short-cuts" to easier responding.

In addition to the use of a blocked design, it was suggested that activations during the interference conditions of Stroop tasks, particularly those in dorsal medial frontal cortex, are commonly ascribed to processing of conflict, but may be a product of simple attention to and time on task (Grinband et al., 2011). Given that basic reaction time differences between MDD patients and healthy volunteers might alter the relative strength of regional activations underlying attention performance, this study also attempted to adjust for differences in reaction time on task related to illness (global slowing) by adjusting for response times in our image analyses.

In this manner, we conducted an fMRI study with a blocked-trial Stroop task controlling reaction time on task to evaluate neural responses to incongruency in subjects with major depressive disorder compared to healthy volunteers.

Methods

Sample

57 subjects with current MDD diagnosed using the Structured Clinical Interview for DSM-IV, Axis I (SCID-I) (Spitzer et al., 1990) and II (SCID-II) (First et al., 1997) and 23 healthy controls (SCID-I, Non-Patient edition) (First et al., 1996) enrolled in this study. Inclusion criteria for MDD subjects included: 1) age 18 to 65 years; 2) capacity to provide informed consent; 3) no significant active physical illness; 4) 17-item Hamilton Depression Rating Scale (HDRS) score greater than or equal to 16; and 5) judged able to tolerate medication washout. Exclusion criteria included: 1) other major psychiatric disorders such as lifetime schizophrenia or schizoaffective disorder, current drug or alcohol abuse (within past 2 months) or drug or alcohol dependence (within past 6 months), anorexia nervosa or bulimia nervosa in the past year, and intravenous drug use or ecstasy use in the past 5 years or more than twice life time; 2) pregnancy, currently lactating, planning to conceive during the course of study participation or abortion in the past two months; 3) cardiac pacemaker, body implant or other metal (e.g., shrapnel or surgical prostheses) in body; 4) a first-degree family history of schizophrenia if the subject was less than 33 years old (mean age of onset for schizophrenia plus two standard deviations); 5) suicidal ideation during the washout phase that warrants admission or requires medication or treatment intervention. Inclusion criteria

for healthy controls included an absence of major psychiatric illness based on SCID (specific phobia permissible), as well as inclusion criteria 1), 2) and 3) from the MDD group and exclusion criteria 1), 2) and 3) from the MDD group.

From this initial sample, we excluded subjects whose error rate on the Stroop task was 25% to reduce noise in the data, because the neural activity of subjects with high error rates is likely to reflect processes other than interference, including lack of attention to task. 11 MDD subjects and 6 controls were excluded for this reason. In addition, we excluded MDD subjects who were prescribed any psychotropic agents except for short-acting benzodiazepines within two weeks of fMRI scanning (4 subjects were excluded for this reason). A final sample of 42 MDD and 17 control subjects were included in analyses.

All participants provided written informed consent prior to participating in the study and the study protocol was approved by the Institutional Review Board of The New York State Psychiatric Institute.

Experimental design

The color-word Stroop task (MacLeod, 1991) was implemented in E-prime (Psychology Software Tools, Inc., Sharpsburg, Philadelphia, <http://www.pstnet.com/eprime.cfm>) on a PC running Windows XP, and was projected on a screen to subjects during fMRI scanning. The block-design task consisted of 12 alternating blocks of color identification trials or incongruent color/word blocks. During color identification blocks, subjects viewed a series of 10 stimuli ('XXXX') and were instructed to identify the font color of each stimulus as quickly as possible (ex. 'XXXX' in blue). Three colors were used – red, blue, and green – and mapped to response keys for, respectively, the index, middle, and ring finger of the right hand. During incongruent color/word blocks, subjects viewed a series of 10 color names presented in an incongruent font color (ex. the word 'red' in blue) and were asked to identify the font color. Each stimulus was displayed for 1900 msec with a 100 msec interstimulus interval; a 12-second rest interval occurred half-way through the task. Subjects registered their responses using an optical response pad with their right hands.

Behavioral Performance

Reaction time and errors were recorded for each trial. Both non-responses and incorrect responses were categorized as errors. Interference rate was calculated as the percent difference in median reaction time between interference and non-interference trials (Keilp, 2008).

Image Acquisition

Functional MRI data were collected on a 3T GE Signa HDx scanner fitted with 8-channel receive-only head coil, using the following parameters: TR = 2000 milliseconds, echo time TE = 28 milliseconds, and flip angle = 90. For each scan, a series of T2*-weighted images with 137 volumes was obtained using interleaved acquisition with a gradient-echo planar sequence with 30 contiguous transversal slices of 4 mm thickness. Matrix size was 64 × 64 pixels with in-plane resolution of 3.75 mm × 3.75 mm and field of view was 24 cm × 24 cm. Head immobilization was established by using head pads within the head coil.

High-resolution anatomical T1-weighted volume scans were obtained during the same scanning session in axial orientation (TR = 7.4 milliseconds, TE = 3.0 milliseconds, flip angle = 9 degree, and field of view = 25.6 cm × 25.6 cm).

Data analysis

The data were preprocessed and analyzed with FMRIB Software Library (FSL, <http://www.fmrib.ox.ac.uk/fsl/>). At the outset of each scan, three dummy images were acquired and discarded prior to analysis. To reduce noise in the analysis, blocks at the beginning or end of the task with >50% error rate were discarded; 1 MDD subject and 2 controls had the initial block discarded due to high error rate, and 10 MDD subjects and 5 controls had the final block discarded due to high error rate.

Raw Echo Planner Image (EPI) data were motion-corrected using MCFLIRT. Data were spatially smoothed using a Gaussian kernel with full width half maximum of 7 mm. A high pass filter cut off of 100 sec was applied to remove low frequency confounds.

For group-level comparisons, individual-subject data were normalized to Montreal Neurological Institute (MNI) space through a three-step normalization using FLIRT; mean EPI images were registered to the first volume of functional acquisition using six degrees of freedom (DOF) as the initial EPI had relatively higher intensity in all images; registration was subsequently performed to the individual's structural T1 image using 7 DOF; the individual T1 was finally registered to MNI space using 12 DOF linear transformation.

Data were analyzed in a whole-brain analysis using a general linear model (GLM) to calculate statistical parametric maps of Z statistics. Single-subject level analysis was performed to create images of parameter estimates using GLM analysis including the following regressors: task blocks (on/off, i.e. comparison between task-blocks and rest), incongruency (on/off, i.e. comparison between incongruent and congruent blocks) and trial-by-trial reaction time, all convolved with the hemodynamic response function, assuming a double-gamma canonical hemodynamic response. Parameter estimates created in the first level analysis were entered into a second-level analysis examining within-group means and between-group contrasts (MDD>controls and controls>MDD) using a Mixed-effects model (FLAME 1 + 2) with outlier de-weighting. In a separate second-level analysis, 24-item HDRS was entered as a regressor to investigate whether BOLD responses to incongruency were associated with depression severity within the MDD group.

Statistical threshold for imaging analysis was set within FSL using a z-score threshold of >2.3 and a corrected cluster threshold of p value <0.05. Comparison of demographic/clinical variables and of behavioral task performance was conducted using t-testing for parametric data, Mann-Whitney U-testing for nonparametric data and chi square testing for categorical data in SPSS (SPSS 19.0, Chicago, Illinois).

Results

Clinical features and behavioral data

Demographic variables including age, sex and handedness did not differ between MDD and controls (table 1). Similarly, behavioral performance on the Stroop task did not differ between MDD subjects and controls included in imaging analysis, as assessed by reaction time, error rate, and interference rate.

Within-Group Analyses

In healthy controls, brain regions activating more during incongruent than congruent blocks included paracingulate gyrus, inferior frontal gyrus, precentral gyrus, middle frontal gyrus, precuneus cortex, lateral occipital cortex, and temporal occipital fusiform gyrus (Fig. 1). A similar pattern of activation was observed in MDD subjects, except for lack of activation of

precuneus cortex during interference trials (Fig 2). Among MDD subjects, depression severity (24-item HDRS) was not associated with bold responses to incongruency.

Group Comparisons

Compared to controls, MDD subjects exhibited lower activation during incongruent blocks across multiple brain regions, including middle frontal gyrus, paracingulate and posterior cingulate, precuneus, occipital regions, and brain stem (Fig 3). No voxels were identified in which MDD subjects were more active than controls during incongruent blocks. Excluding MDD subjects with a history of prior suicide attempt ($n = 9$) from the analysis did not significantly affect the findings reported here (data not shown). Furthermore, comparison of suicide attempters ($N = 9$) and non-suicide attempters ($N = 33$) did not show any brain regions that were activated or deactivated with statistical significance between those two groups.

Discussion

This is the largest study to date examining the neural correlates of Stroop performance in MDD. Despite comparable task performance to controls on the task used in this study, MDD subjects demonstrated less activity across a broadly-distributed network of brain regions during the interference condition. Regions less active during interference in MDD included: middle frontal gyrus, associated with executive control/movement planning (Clark et al., 2010); middle temporal gyrus, which plays a role in semantic processing (Demonet et al., 1992; Maess et al., 2002); and lingual gyrus, containing secondary visual cortex. The latter two regions have previously been reported to be involved in Stroop task performance (Carter et al., 1995; Pardo et al., 1990; Peterson et al., 2002; Roelofs and Hagoort, 2002). These findings suggest that brain regions related to executive function, visual processing, and semantic processing are less active during this specific cognitive task in MDD subjects than in healthy controls. This finding is consistent with a larger literature regarding cognitive deficits in MDD (Marazziti et al., 2010).

Our findings differ from Wagner et al. (Wagner et al., 2006) in that we found MDD subjects to manifest widespread impaired activation during interference processing relative to healthy volunteers. The most likely explanation for this difference is the use of a block design, which required participants to not only respond to an incongruent stimulus, but to maintain that level of responding for a set of stimuli presented over 20 seconds. Our findings of lower activation in MDD subjects in a longer block of trials is consistent with behavioral data suggesting that performance often lags in depressed patients over time on a given task due to difficulty maintaining an appropriate level of arousal (Cohen et al., 2001). This would suggest that there may not be a deficit in MDD relative to controls in initial task processing but with subsequent trials a deficit emerges as their activation declines relative to healthy controls. Furthermore, the Stroop task in the Wagner et al. study was atypical in that response options were presented in a multiple-choice format, with two possible response options on the left and right of the screen, below the target stimulus, in an effort to reduce the need to memorize key presses using a manual response.

Another possible explanation of our findings relates to the comparison condition employed in this Stroop task. The comparison condition was a color-naming condition, not a congruent word condition; this may have accentuated differences between the two task conditions, and therefore highlighted the difference between healthy volunteers and MDD patients. In the WEAVER++ model for the Stroop task (fig 4) (Roelofs and Hagoort, 2002), executive control in Stroop tasks is hypothetically composed of two factors: input control and goal control, which operate at the level of word-form perception and conceptual identification after color perception. Thus, incongruent color/word stimuli require two executive control

components, while simple color identification condition requires only one (congruent color/word, presented in a randomly ordered, mixed-trial design, requires two). Therefore superior functioning of executive control in non-patients would be reflected in a higher degree of relative activation in the interference vs. color-naming condition. Accentuating the differences between conditions may have accentuated differences between groups.

As mentioned above, interference resolution during the Stroop task is related to the risk for suicidal behavior (Keilp et al., 2008). The MDD sample examined in this study included nine subjects with a history of prior suicide attempt. However, as described in the results section, our findings do not appear to be driven by suicide history and do not show significant differences between suicide attempters and non-suicide attempters. It might be because that there are too few suicide attempters ($N = 9$) in this sample to draw any definitive conclusions about the nature of Stroop response in past attempters.

With regard to the behavioral performance of our subjects, our previous neuropsychological study of Stroop task performance in MDD identified differences in interference processing (Keilp et al., 2008), whereas we did not observe behavioral differences in interference processing between MDD subjects and controls in the current study. In the current study, we excluded both subjects and individual blocks (at the beginning or end of the task) with high error rates, in order to reduce noise in the fMRI data. However, this did not explain the difference in behavioral findings between these two studies, as we still observed no differences in reaction time between groups even when including all subjects and blocks irrespective of error rate (mean reaction time: 694.9 milliseconds in 53 MDD and 644.4 milliseconds in 23 controls; error rate: 13.6% and 20.4%, $p = 0.14, 0.26$, respectively). More importantly, the task used in our previous behavioral studies was self-paced, with a short interstimulus interval (new stimuli appeared 50 milliseconds after a response, making overall block rate more rapid) and employed auditory feedback on each trial, insuring that participants would be attentive to making frequent errors. This auditory feedback was eliminated in the current imaging study, and despite practice prior to entering the scanner, participants in this imaging study exhibited much higher error rates than in our behavioral studies.

Limitations

While all subjects were antidepressant-free for a minimum of two weeks at the time of scanning, not all MDD subjects were antidepressant-naïve. However, we obtained similar results when data was reanalyzed including only antidepressant-naïve subjects in the MDD sample, i.e. 25 drug naïve MDD subjects showed deactivation in almost the same regions in comparison with healthy controls as were observed when comparing the entire MDD sample to controls.

Conclusions

In conclusion, our study provides support for specific neural abnormalities in MDD during cognitive processing. Further studies may clarify whether the abnormalities identified in this study represent a trait or state deficit. Additionally, the discrepancy between event-related and blocked-trial interference processing in MDD subjects during the Stroop Task suggests that less activity may be a function of demand inherent in the current task of maintaining arousal over time. Deficits in MDD in attention, therefore, may not be the product of dysfunction on any single trial, but of a failure to maintain levels of activation over multiple trials. Further research is needed, in the form of a direct comparison of single event vs. massed event stimulus presentations in the same subjects.

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References

- Carter CS, Mintun M, Cohen JD. Interference and facilitation effects during selective attention: an H215O PET study of Stroop task performance. *Neuroimage*. 1995; 2:264–272. [PubMed: 9343611]
- Clark, DL.; Boutros, NN.; Mendez, MF. The brain and behavior: an introduction to behavioral neuroanatomy. Cambridge University Press; New York: 2010.
- Cohen R, Lohr I, Paul R, Boland R. Impairments of attention and effort among patients with major affective disorders. *J Neuropsychiatry Clin Neurosci*. 2001; 13:385–395. [PubMed: 11514646]
- Demonet JF, Chollet F, Ramsay S, Cardebat D, Nespoulous JL, Wise R, Rascol A, Frackowiak R. The anatomy of phonological and semantic processing in normal subjects. *Brain*. 1992; 115 (Pt 6):1753–1768. [PubMed: 1486459]
- First, MB.; Spitzer, RL.; Gibbon, M.; Williams, JBW. Structured Clinical Interview for DSM-IV Axis I Disorders, Research Version, Non-patient Edition. New York State Psychiatric Institute; New York, NY: 1997.
- First, MB.; Spitzer, RL.; Gibbon, M.; Williams, JBW.; Loma, B. Structured Clinical Interview for DSM-IV Axis II Personality Disorders (SCID-II), (Version 2.0). Biometric Research Department, New York State Psychiatric Institute; New York, NY: 1996.
- Grinband J, Savitskaya J, Wager TD, Teichert T, Ferrera VP, Hirsch J. The dorsal medial frontal cortex is sensitive to time on task, not response conflict or error likelihood. *Neuroimage*. 2011; 57:303–311. [PubMed: 21168515]
- Keilp JG, Gorlyn M, Oquendo MA, Burke AK, Mann JJ. Attention deficit in depressed suicide attempters. *Psychiatry Res*. 2008; 159:7–17. [PubMed: 18329724]
- Keilp JG, Sackeim HA, Brodsky BS, Oquendo MA, Malone KM, Mann JJ. Neuropsychological dysfunction in depressed suicide attempters. *Am J Psychiatry*. 2001; 158:735–741. [PubMed: 11329395]
- Killgore WD, Gruber SA, Yurgelun-Todd DA. Depressed mood and lateralized prefrontal activity during a Stroop task in adolescent children. *Neurosci Lett*. 2007; 416:43–48. [PubMed: 17350756]
- Legris J, Links PS, van Reekum R, Tannock R, Toplak M. Executive function and suicidal risk in women with Borderline Personality Disorder. *Psychiatry Res*. 2012
- Leung HC, Skudlarski P, Gatenby JC, Peterson BS, Gore JC. An event-related functional MRI study of the stroop color word interference task. *Cereb Cortex*. 2000; 10:552–560. [PubMed: 10859133]
- MacLeod CM. Half a century of research on the Stroop effect: an integrative review. *Psychol Bull*. 1991; 109:163–203. [PubMed: 2034749]
- MacLeod CM, Sheehan PW. Hypnotic control of attention in the Stroop task: a historical footnote. *Conscious Cogn*. 2003; 12:347–353. [PubMed: 12941282]
- Maess B, Friederici AD, Damian M, Meyer AS, Levelt WJ. Semantic category interference in overt picture naming: sharpening current density localization by PCA. *J Cogn Neurosci*. 2002; 14:455–462. [PubMed: 11970804]
- Marazziti D, Consoli G, Picchetti M, Carlini M, Faravelli L. Cognitive impairment in major depression. *Eur J Pharmacol*. 2010; 626:83–86. [PubMed: 19835870]
- Mead LA, Mayer AR, Bobholz JA, Woodley SJ, Cunningham JM, Hammeke TA, Rao SM. Neural basis of the Stroop interference task: response competition or selective attention? *J Int Neuropsychol Soc*. 2002; 8:735–742. [PubMed: 12240737]

- Murrough JW, Iacoviello B, Neumeister A, Charney DS, Iosifescu DV. Cognitive dysfunction in depression: neurocircuitry and new therapeutic strategies. *Neurobiol Learn Mem.* 2011; 96:553–563. [PubMed: 21704176]
- Nee DE, Wager TD, Jonides J. Interference resolution: insights from a meta-analysis of neuroimaging tasks. *Cogn Affect Behav Neurosci.* 2007; 7:1–17. [PubMed: 17598730]
- Pardo JV, Pardo PJ, Janer KW, Raichle ME. The anterior cingulate cortex mediates processing selection in the Stroop attentional conflict paradigm. *Proc Natl Acad Sci U S A.* 1990; 87:256–259. [PubMed: 2296583]
- Peterson BS, Kane MJ, Alexander GM, Lacadie C, Skudlarski P, Leung HC, May J, Gore JC. An event-related functional MRI study comparing interference effects in the Simon and Stroop tasks. *Brain Res Cogn Brain Res.* 2002; 13:427–440. [PubMed: 11919006]
- Peterson BS, Skudlarski P, Gatenby JC, Zhang H, Anderson AW, Gore JC. An fMRI study of Stroop word-color interference: evidence for cingulate subregions subserving multiple distributed attentional systems. *Biol Psychiatry.* 1999; 45:1237–1258. [PubMed: 10349031]
- Roberts KL, Hall DA. Examining a supramodal network for conflict processing: a systematic review and novel functional magnetic resonance imaging data for related visual and auditory stroop tasks. *J Cogn Neurosci.* 2008; 20:1063–1078. [PubMed: 18211237]
- Roelofs A, Hagoort P. Control of language use: cognitive modeling of the hemodynamics of Stroop task performance. *Brain Res Cogn Brain Res.* 2002; 15:85–97. [PubMed: 12433384]
- Sneed JR, Roose SP, Keilp JG, Krishnan KR, Alexopoulos GS, Sackeim HA. Response inhibition predicts poor antidepressant treatment response in very old depressed patients. *Am J Geriatr Psychiatry.* 2007; 15:553–563. [PubMed: 17586780]
- Spitzer, RL.; Williams, JBW.; Gibbon, M.; First, MB. *Instruction Manual for the Structured Clinical Interview for the DSM-IV (SCID-P).* American Psychiatric Press; Washington, DC: 1990.
- Veiel HO. A preliminary profile of neuropsychological deficits associated with major depression. *J Clin Exp Neuropsychol.* 1997; 19:587–603. [PubMed: 9342691]
- Wagner G, Sinsel E, Sobanski T, Kohler S, Marinou V, Mentzel HJ, Sauer H, Schlosser RG. Cortical inefficiency in patients with unipolar depression: an event-related FMRI study with the Stroop task. *Biol Psychiatry.* 2006; 59:958–965. [PubMed: 16458263]
- Zakzanis KK, Leach L, Kaplan E. On the nature and pattern of neurocognitive function in major depressive disorder. *Neuropsychiatry Neuropsychol Behav Neurol.* 1998; 11:111–119. [PubMed: 9742509]

Figure 1. Incongruent > congruent blocks in healthy controls

Healthy controls showed brain regions activating more during incongruent than congruent blocks: paracingulate gyrus, inferior frontal gyrus, precentral gyrus, middle frontal gyrus, precuneus cortex, lateral occipital cortex, and temporal occipital fusiform gyrus ($Z > 2.3$, corrected $p < 0.05$).

Figure 2. Incongruent > congruent blocks in MDD subjects

MDD subjects showed brain regions activating more during incongruent than congruent blocks: paracingulate gyrus, inferior frontal gyrus, precentral gyrus, middle frontal gyrus, lateral occipital cortex, and temporal occipital fusiform gyrus ($Z > 2.3$, corrected $p < 0.05$). MDD, major depressive disorders.

Figure 3. Healthy controls > MDD subjects in incongruency

Healthy controls exhibited higher activation compared to MDD subjects: middle frontal gyrus, paracingulate and posterior cingulate, precuneus, occipital regions and brain stem ($Z > 2.3$, corrected $p < 0.05$). MDD, major depressive disorders.

Figure 4.
Flow of information and control in the WEAVING++ model (Roelofs and Hagoort, 2002)

Table 1

Participants Demographics and Behavioral Data on Task

	Patients with Depression		Controls	P value ^a
Participants	N, %	42	17	100.0
Sex, Female	N, %	26	9	52.9
Age, yo	mean, SD	36.2	30.8	0.569
Handedness, Right	N, %	35	16	8.3
Depressive Episodes, N	mean, SD	3.5	0.0	94.1
Suicide Attempts, N	mean, SD	0.48	0.0	0.0
Absolute Drug Naïve	N, %	18	-	-
24-item HDRS	mean, SD	24.3	2.4	-
Hopelessness Score	mean, SD	9.4	1.5	2.6
Global Assessment Scale	mean, SD	57.2	89.2	1.5
RT on Task in Color tasks, msec	median, range	607.3	596.7	5.0
RT on Task in Color/Word tasks, msec	median, range	731.6	714.2	0.001 *
Interference rate ^b , %	mean, SD	20.1	19.5	0.828
Error rate in all tasks, %	mean, SD	7.0	8.6	0.967
Error rate in Color tasks, %	mean, SD	4.9	7.2	0.889
Error rate in Color/Word tasks, %	mean, SD	9.0	10.1	0.412
				0.180
				0.709

^a P value was analyzed by t-test for continuous parametric variables, Mann-Whitney U-test for continuous nonparametric variables and by chi square test for categorical variables

^b Interference rate = ((median reaction time in color/word tasks) – (median reaction time in color tasks))/(median reaction time in color tasks)

HDRS, Hamilton Depression Rating Scale; RT, Reaction time