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Atrophy in two attention networks is associated with performance on a Flanker task in neurodegenerative disease

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Abstract

This study investigated the neurobiological basis of attentional control dysfunction in neurodegenerative disease by determining the effect of regional brain atrophy on Flanker task performance of neurodegenerative patients. We hypothesized that atrophy in DLPFC and ACC would be significantly associated with decreased attentional control performance on the Flanker task. We used voxel-based morphometry (VBM) to measure the relationship between MRI measures of regional grey matter atrophy and performance on a version of the Flanker task, measured by accuracy and response time. Sixty-five subjects participated, including patients with frontotemporal dementia, Alzheimer's disease, mild cognitive impairment, non-fluent progressive aphasia, corticobasal degeneration, progressive supranuclear palsy, semantic dementia, and healthy controls. Accuracy measures of attentional control and response time measures of attentional control were associated with two different patterns of regional atrophy across subjects. First, there was an association between left hemisphere DLPFC and ACC atrophy and poorer attentional control accuracy. Second, right hemisphere temporal-parietal junction (TPJ) and ventrolateral prefrontal cortex (VLPFC) and DLPFC atrophy were associated with slower response times during attentional control on accurate trials, which may reflect emergent involvement due to deficits in the DLPFC-ACC network.

Introduction

Clinical descriptions and empirical studies of patients with neurodegenerative disease have highlighted the presence of "executive function" symptoms such as confusion, distractibility, poor planning, and deficits in carrying out goal-directed behavior (Miller and Cummings, 2007). Measures of executive function are the best predictor of a patient's score on Indices of Daily Living, which measure how well patients are able to maintain quality of life during disease progression (Cahn-Weiner et al., 2007). Executive deficits can underlie

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memory and learning dysfunction (Matuszewski et al., 2006; Wicklund et al., 2006), and are associated with lack of disease insight and difficult patient-caregiver relationships.

One important executive function is attentional control. Attentional control is the goal-driven allocation of attention toward the processing of task-appropriate stimuli and responses, particularly when we experience competition, or “conflict”, between the processing of task-relevant information and items that distract us. Effective attentional control is dependent upon self-monitoring mechanisms to determine whether behavioral goals are met, or whether additional efforts are required. While many of the abnormal social and cognitive behaviors observed in neurodegenerative patients may result from progressive deficits of attentional control, the neurobiological bases for these attention dysfunctions in neurodegenerative disease are largely unknown.

In the healthy brain, there is evidence that attentional control processes are mediated by a large-scale network involving frontal and parietal systems that interact with sensory and motor areas (e.g. Mesulam, 1981; Posner and Petersen, 1990; Banich et al., 2000; Miller and Cohen, 2001). This network is particularly engaged in situations in which goal-relevant response selection is made difficult by competition from other responses (Paus et al., 1998; Rafal et al., 1996). This competition can arise because one response is task relevant, but the other has stronger bottom-up salience, such as on the Stroop task (MacDonald et al., 2000) or one was previously correct but is now incorrect, such as in tasks which switch response rules from trial to trial (Swainson et al., 2003; Konishi et al., 2001; Dove et al., 2000) or in go/no go tasks (de Zubizaray et al., 2000; Kiehl et al., 2000; Braver et al., 2001; Durston et al., 2002) or because both are associated with correct responses generally, but some additional component of the task specifies one as correct for each trial, such as in the Flanker task (Casey et al., 2000; Botvinick et al., 1999; van Veen and Carter, 2002; Kornblum et al., 1990; Fitts, 1959, Stroop, 1935). In the flanker task, subjects must identify the direction of the center arrow flanked by incongruent or congruent stimulus arrays (Eriksen and Eriksen, 1974).

These tasks have been used in functional neuroimaging studies of the healthy brain to investigate the specific roles of the frontal and parietal areas and how these areas may work together to mediate attentional control. fMRI studies of conflict tasks suggest that ACC may respond when stimulus or response conflict is present (Cohen et al., 2000; Hazeltine et al., 2000). Botvinick et al. (1999) proposed that ACC monitors for response conflict during stimulus processing, and triggers DLPFC to increase attention to the task-appropriate processes associated with the correct response in that trials (Carter et al., 1998; Cohen et al., 2000). Kerns et al. (2004) provide direct evidence for a relationship between ACC activity and compensatory DLPFC activity on the subsequent trial (i.e. subsequent preparatory activity). ACC activity on incongruent (high conflict) trials correlated with DLPFC activity on the subsequent trial. This finding suggests that preparatory functions in DLPFC increase to compensate for conflict on the previous trial, in direct or indirect response to conflict-related activity in ACC. Overall, the functional neuroimaging literature suggests that DLPFC is responsible for maintenance of task demands and preparatory deployment of attention, and ACC is responsible for monitoring performance in order to detect cognitive and behavioral conditions with potential negative outcomes, and triggering DLPFC to increase attention or change behavior. These increases in attention to resolve conflicting stimulus and response activations are also often associated with increases in activity in ventrolateral prefrontal cortex (VLPFC) and the intraparietal sulcus region (IPS) (Forstmann et al., 2008). IPS has been implicated in the deployment and sustaining of visuospatial attention (e.g. Corbetta and Shulman, 2002; Yantis et al., 2002; Beauchamp et al., 2001; Vandenberghe et al., 2001). VLPFC has been associated with response-inhibition, rule-

learning and task-shifting (e.g. Aron et al., 2004; Bunge, 2004; Hampshire and Owen, 2006; Crone et al., 2006; Brass and von Cramon, 2002).

The networks involved in cognitive control deficits in neurological patients are likely to be complex and to date are poorly understood. This study investigated the neurobiological basis of attentional control dysfunction in neurodegenerative disease by determining the effect of regional brain atrophy on Flanker task performance of neurodegenerative patients. We hypothesized that atrophy in DLPFC and ACC would be significantly associated with decreased attentional control performance on the Flanker task. Attentional control performance is assessed by the relative accuracy and response time performance in the congruent and incongruent Flanker stimulus conditions. A decrease in attentional control performance is indicated by a selective decrease in accuracy and longer response times in the incongruent condition, relative to the congruent condition. We used voxel-based morphometry (VBM) to measure the relationship between MRI measures of regional grey matter atrophy and performance on a version of the Flanker task, measured by accuracy and response time. Patients from diverse diagnostic groups with variable Flanker task performance and patterns of grey matter atrophy were included to provide variability in the sample and improve the power of the correlation analysis. Examining patients with variable clinical symptoms and atrophy patterns also indicates the degree to which a correlation between regional atrophy and performance holds across diagnostic categories, and is thus a more generalizable reflection of the relationship between task performance and regional brain dysfunction independent of diagnostic categories or typical overall patterns of atrophy associated with those categories.

Methods

Subjects

Sixty-five subjects were recruited from a pool of UCSF Memory and Aging Center research participants, and gave written informed consent in accordance with the UCSF IRB. Each subject underwent a comprehensive diagnostic evaluation, including a neurological exam, cognitive screening, and informant report. Research diagnosis was determined by a multidisciplinary team. The subjects ranged in age from 44 years of age to 81 years of age (Mean: 63.9 years, StDev: 8.8 years). These included 11 patients with Frontotemporal Dementia (FTD) (Neary, 1995), 6 patients with Alzheimer's Disease (AD) (McKhann et al., 1984), 8 patients with Mild Cognitive Impairment (MCI) (Petersen, 2006), 2 patients who met the criteria for Non-Fluent Progressive Aphasia (NPFA) (Gorno-Tempini et al., 2004), 2 patients who met the criteria for Corticobasal Degeneration (CBD) (Litvan et al., 1996), 3 patients who met the criteria for Progressive Supranuclear Palsy (PSP) (Litvan et al., 1996), and 10 patients who met the criteria for Semantic Dementia (SD) (Neary, 1995). In addition, the study sample included 22 age-matched healthy controls (HC) who were evaluated by the same UCSF diagnostic team. For inclusion as healthy controls for this study, subjects had to have a normal neurological exam, a Clinical Dementia Rating (CDR) scale score = 0, and a Mini-Mental State Examination (MMSE) score >28 (of 30) (Table 1).

Flanker Task

The Flanker task requires subjects to identify the direction of the center arrow in a row of five arrows by pressing a button on a response box corresponding to the direction of the center arrow (left or right). This version of the Flanker task has two conditions: a congruent condition, in which all arrows point in the same direction as the center arrow, and an incongruent condition, in which the center arrow is surrounded (or flanked) by arrows pointing in the opposite direction on each side (Figure 1). Stimuli were presented foveally on a computer screen for a duration of 2 seconds using E-Prime (www.psnet.com). A total

of 64 stimuli were presented in each condition in random order. Correct performance in the incongruent condition is well known to require greater attentional control than the congruent condition, as subjects must inhibit the processing and response associated with the distracting flanker stimuli. Thus, comparison of the regional brain atrophy associated with performance in the incongruent condition, while controlling for regional brain atrophy associated with performance in the congruent condition, identifies atrophy selectively associated with deficits in attentional control.

Accuracy and response times were recorded for each trial, and the percent correct and median response time from accurate responses for each condition were calculated for each subject. We used median response time rather than mean because response time distributions tend to be skewed, and the median is less sensitive to this asymmetry. Only subjects who were greater than 50% accurate were included in the study. This relatively low threshold was selected for the accuracy analysis in order to allow for the greatest reasonable range of accuracy performance. The response time analyses were performed both on this full sample of 65 subjects, and on only subjects who were greater than 70% accurate, out of concern that response times for correct trials might still reflect guessing rather than true task performance in subjects with accuracy under 70%. This higher threshold excluded 6 subjects (n=59). The pattern of results was not qualitatively different in the full and reduced samples, and therefore we report the results for the full sample of 65 subjects for both accuracy and response time analyses, for ease of comparison. [U1]

MR Image Acquisition

A T1 weighted structural MR was acquired for each subject using an MPRAGE sequence on a 1.5-T Magnetom VISION system (Siemens, Iselin, NJ), (TR/TE/TI = 10/4/300 ms, flip angle=15). The in-plane coronal resolution and slice thickness were 1.0×1.0 and 1.5mm respectively.

Statistical Analyses

Behavioral analyses

Percent Correct scores were submitted to a repeated measures analysis of variance (ANOVA) with diagnostic group as a between subjects factor (patients, healthy controls) and congruency condition as a within subjects factor (congruent, incongruent). Similarly, median response times were submitted to a repeated measures analysis of variance (ANOVA) with diagnostic group as a between subjects factor and congruency condition as a within subjects factor (congruent, incongruent). We used post-hoc t tests to examine the interactions.

VBM analyses

A general linear model analysis was performed with congruent condition percent correct, incongruent condition percent correct and age as covariates, and total intracranial volume as a global variable to control for differences in head size. An ANCOVA global normalization was used, with a grand mean scaling factor was .64, equal to the mean of total gray matter volume across all subjects. The absolute threshold masking was 0.05. T-tests were performed to identify voxels with a significant relationship between regional grey matter volume and superior performance on the incongruent condition, relative to the congruent condition. This effectively reveals atrophy associated with attentional control. Each contrast was thresholded at a p value of 0.05 and cluster size of 20 voxels, after FDR correction for multiple comparisons. FWE correction for multiple comparisons was also calculated, but no clusters reached significance at this more conservative level. A similar general linear model analysis was performed with congruent condition median response time, incongruent

condition median response time and age as covariates, and total intracranial volume as a global variable to control for differences in head size. For this analysis, each contrast was thresholded at a p value of 0.05 and cluster size of 20 voxels, after FWE correction for multiple comparisons. A more stringent correction for multiple comparisons was used for the median RT analysis than the accuracy analysis because at a p value of .05 with FDR correction, nearly all voxels in the brain show a significant relationship between volume and attentional control. This is reflective of the increase in variability range associated with the median RT relative to the percent correct.

Results

Flanker Accuracy

The results of the ANOVA of percent correct with group as a between-subjects factor (patients, healthy controls), congruency (congruent, incongruent) as a within-subjects factor revealed a significant main effect of congruency ($F[1,7] = 7.202, p < .009$). Subjects were more accurate in the congruent condition than the incongruent condition. There was also a significant main effect of group ($F[1,7] = 7.86, p < .007$), indicating that there were differences in overall accuracy between groups.

There was also a significant group by congruency interaction ($F[1,7] = 5.247, p = .025$), indicating that patients showed greater conflict-related accuracy effects than healthy controls. Post-hoc t tests of congruency within groups revealed that congruency effects were significant in the patient group ($t = 3.5, p = .001$), while there was a trend towards a congruency effect in the healthy controls ($t = 1.856, p = .077$). (Table 2, shows the breakdown of accuracy performance by diagnosis within the patient group. We did not analyze differences between these more specific diagnostic groups because of the small number of subjects in many of these groups).

VBM

Poorer accuracy during attentional control (i.e. fewer correct responses in the incongruent condition, relative to the congruent condition) on the Flanker task was associated with atrophy in the lateral prefrontal cortex bilaterally (primarily on the left), including DLPFC, extending to the frontal pole and to orbitofrontal cortex, and with atrophy in the left anterior cingulate cortex (ACC), and right cerebellum (Figure 2a, Table 3).

Flanker Response Time

The results of the ANOVA of median RT with group as a between-subjects factor (patients, healthy controls), congruency (congruent, incongruent) as a within-subjects factor revealed a significant main effect of congruency ($F[1,7] = 175.89, p < .001$). Subjects responded more quickly in the congruent condition than the incongruent condition. There was also a significant main effect of group ($F[1,7] = 14.39, p = .001$), indicating that healthy controls responded more quickly than patients. (Table 4). The congruency by group interaction was not significant.

VBM

Poorer response times during attentional control (i.e. slower response times in the incongruent condition, relative to the congruent condition) within accurate trials of the Flanker task were associated with atrophy in bilateral DLPFC, right VLPFC and right temporal-parietal junction (TPJ) (Figure 2b).

Discussion

We found that accuracy measures of attentional control and response time measures of attentional control were associated with two different patterns of regional atrophy across subjects. First, there was an association between left hemisphere DLPFC and ACC atrophy and poorer attentional control accuracy. Second, right hemisphere TPJ, VLPFC and DLPFC atrophy were associated with slower response times during attentional control on accurate trials. These patterns of atrophy correlated with task performance reflect the involvement of two attention networks that have been well-established in the healthy brain by functional imaging literature (e.g. Cohen et al., 2000; Corbetta and Shulman, 2002). These results highlight the importance of these regions in attentional control and the utility of the flanker paradigm for identifying patients with dysfunction in these regions.

The association between attentional control and DLPFC and ACC atrophy confirms our hypothesis that this network is associated with deficient attentional control in neurodegenerative patients. This network is believed to mediate top-down attentional control, with ACC monitoring for conflict and DLPFC (perhaps together with ACC) responsible for maintaining task demands and allocating attention accordingly both in preparation for stimulus presentation, and during stimulus processing and response selection (Luks et al., 2007; Luks et al., 2002; MacDonald et al., 2000; Weissman et al., 2004; Banich et al., 2000; Cohen et al., 2000; Carter et al., 2000; Mayr et al., 2003; Bunge et al., 2005; Miller and Cohen, 2001). Greater atrophy in this network was associated with a greater percentage of errors in the incongruent condition, relative to the congruent condition, indicating a greater inability to correctly direct attention to the central arrow and inhibit attention to the flanking arrows, and to detect and resolve conflict between these stimuli correctly.

More surprising is the strong relationship between response time measures of attentional control and atrophy in the right VLPFC and right TPJ. This predominately right-hemisphere network has been well-established in the healthy control functional imaging literature (Corbetta and Shulman, 2002; Shulman et al., 2007; Kincade et al., 2005). This network is thought to be responsible for reorienting attention towards salient stimuli, in a bottom-up fashion, particularly for novel or infrequent but task-relevant stimuli. However, the flanker task does not involve the presentation of novel or infrequent stimuli, and activity in this TPJ-VLPFC network has not been reported in healthy adults during fMRI flanker conflict, or other tasks that create cognitive conflict, such as the classic Stroop task. Rather, these studies report DLPFC, ACC activity (eg. Cohen et al., 2000; MacDonald et al., 2000, Banich et al., 2000), although there is evidence that TPJ lesions are associated with impaired attentional control on the flanker task (Ro et al. 1998).

One possible reason for the difference between the relationship that we report between task performance and brain networks and the relationship between task activity and brain networks reported in the healthy functional imaging literature may be that here we are specifically looking at regions that relate to the speed of correct performance during attentional control, while most fMRI studies have looked at areas that are active generally during correct performance, regardless of response speed. However, there have been a few studies that have related response times to functional activity, and reported ACC or DLPFC correlates, but no additional TPJ-VLPFC activity (e.g. Kerns et al., 2004).

Another possible explanation for our TPJ-VLPFC network finding is that attentional control in neurodegenerative patients is associated with the use of multiple strategies of task performance to compensate for functional deficits. In healthy subjects, flanker task performance is accomplished by maintaining task demands (attend center, ignore flankers)

and allocating preparatory attention prior to stimulus presentation. When conflict is detected in the incongruent condition, due to processing of the flankers as well as the central stimulus and the activation of competing responses (Kornblum et al., 1990), healthy subjects use this maintained task demand information to select the correct response. These task maintenance, preparatory attention, and conflict monitoring processes are normally mediated by the DLPFC-ACC network (Luks et al., 2007; Kerns et al., 2004; Weissman et al., 2004). However, the accuracy results here indicate that atrophy in the DLPFC-ACC network was associated with significant disruption of these attention functions. In the absence of an efficient top-down attentional control system mediated by the DLPFC-ACC network (or during attentional lapses in that network in subjects with more intact DLPFC-ACC networks), accurate and speedy processing of incongruent flanker task stimuli may be accomplished by the stimulus-driven, bottom-up reorienting and inhibitory mechanisms of the TPJ-VLPFC network. In other words, when top-down attentional control systems are impaired, limiting the degree to which subject can use preparatory attention and maintenance of task information to “expect” incongruent stimuli, these stimuli may be treated as “unexpected” stimuli. In this case, TPJ may be responsible for reorienting attention to the incongruent stimuli, and VLPFC may be responsible for inhibiting the response associated with flanker arrows (Forstmann et al., 2008; Aron et al., 2004). Thus, in the absence of effective DLPFC-ACC top-down attentional control functions, the speed with which subjects respond correctly in the incongruent condition may reflect the integrity of these bottom-up attention systems.

Another interesting aspect of the current results is the degree to which the associations between atrophy and task performance reported here are not simply mirrors of more general associations between atrophy and particular disease diagnoses. Comparisons of regional atrophy between diagnostic groups and healthy control subjects revealed significant parietal atrophy in AD patients, but in IPS/superior parietal, not TPJ, consistent with previous reports (Boxer et al., 2003). Both FTD and SD patients had substantial temporal lobe atrophy, also consistent with previous reports, although DLPFC and ACC atrophy are also reported in FTD, CBD and PNFA patients (Rosen et al., 2002a; Boxer et al., 2003). Thus, our results reveal that both behavioral and neurobiological impairments in attentional control occurred across diagnostic groups, even in patients for whom atrophy in the DLPFC-ACC and TPJ-VLPFC networks is not a defining characteristic of their disease. To further investigate these issues, our future studies include functional neuroimaging investigations of regional brain activity during performance of the flanker task in dementia patients and healthy controls.

Conclusion

In conclusion, we found that the atrophy in the DLPFC-ACC network was associated with reductions in accurate attentional control, and that atrophy in the TPJ-VLPFC network was associated with slower attentional control. Dysfunction in these networks and in attentional control can occur in diagnostic groups for which attentional deficits and frontal atrophy are not primary diagnostic features. Furthermore, cognitive deficits in neurodegenerative disease may reflect not only damage to systems that meet those cognitive demands in the healthy brain, but may reflect emergent deficits as the damaged brain attempts to compensate for its functional deficits by engaging alternate cognitive strategies, which may be mediated by other brain regions which are also impaired. These findings are clinically relevant because executive functions, including attentional control, are associated with quality of life, ability to perform daily living tasks, and caregiver condition, and therefore the integrity of these cognitive functions and the integrity of the neurobiological networks that mediate them are important in all neurodegenerative populations. Understanding of the biological bases of

cognitive deficits in neurodegenerative disease aids the development of therapeutic behavioral coping strategies and guides treatment development .

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Figure 1.

Figure 2.

Table 1

Subject Demographics

Group	N	Mean Age (stdev)	Mean MMSE (stdev)	Gender M / F
AD	6	62 (7)	27 (.8)	4 / 2
CBD	2	69 (6)	28 (0)	1 / 1
FTD	11	61 (8)	27 (2.9)	8 / 3
MCI	9	66 (8)	29 (1)	6 / 3
NC	22	64 (12)	29 (.7)	12 / 10
PNFA	2	61 (6)	27 (0)	1 / 1
PSP	3	65 (8)	27 (4.2)	1 / 2
SD	10	65 (5)	24 (5.8)	6 / 4

Table 2

Accuracy and Response Time Results

Group	Congruent Mean Percent Correct (stdev)	Incongruent Mean Percent Correct (stdev)	Congruent Mean Median Response Time (stdev)	Incongruent Mean Median Response Time (stdev)
AD	89.1 (18.8)	65 (30.2)	883 (108.5)	1076 (123.1)
CBD	84.4 (19.9)	69 (37.6)	1133 (398.8)	1215 (443.4)
FTD	96.2 (6.4)	82.8 (27.6)	778 (125.1)	963 (197.9)
MCI	99.5 (.8)	99.0 (1.7)	828 (96)	1019 (103.3)
NC	99.5 (.9)	98.7 (1.7)	938 (94.6)	1076 (110.0)
PNFA	99.2 (1.1)	99.3 (1.1)	905 (42.1)	1055 (93.7)
PSP	86.5 (10.2)	69.3 (15.8)	706 (374.2)	832 (340.1)
SD	98.1 (2.7)	93.6 (8.8)	685 (190.6)	814 (160.4)

Table 3

VBM Flanker Accuracy Results

Area	BA	X	Y	Z	Number of Voxels	T value
Left PFC	46	-27	52	16	5015	4.62
Right OFC	47	36	29	-16	211	4.44
Right Cerebellum		43	-77	-33	79	3.89
Right OFC	10	38	53	-1	101	3.83
Right PFC	10	26	54	15	54	3.59
Left ACC	32	-5	21	36	60	3.54

Table 4

VBM Flanker Response Time Results

Area	BA	X	Y	Z	Number of Voxels	T value
Right TPJ	21	52	-55	8	3667	5.57
Right VLPFC	46	41	51	4	435	5.23
Right DLPFC	9	39	33	35	464	5.00
Left DLPFC	9	-42	20	39	61	4.93
Right PFC	8	27	20	48	23	4.75