Inefficient response inhibition in individuals with mild cognitive impairment

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Received 13 February 2006; received in revised form 2 November 2006; accepted 10 November 2006

Available online 18 December 2006

Abstract

Individuals diagnosed with mild cognitive impairment (MCI) show primary deficits in memory and are at increased risk for developing Alzheimer’s disease (AD). In light of recent evidence that executive cognitive deficits are common in AD and may be detectable in individuals diagnosed with MCI, we extend these findings to the investigation of response inhibition, an essential aspect of executive cognitive control. Twenty MCI patients and 20 healthy controls (HC) completed an arrow version of the flanker task [Eriksen, B. A., & Eriksen, C. W. (1974). Effects of noise letters upon the identification of target letters in a non-search task. *Perception & Psychophysics*, 16, 143–149] in which participants responded to a target arrow surrounded by distractors (i.e., flankers) that signaled a same (congruent) or a conflicting (incongruent) response. Reaction time (RT) increased in both groups when flankers signaled an incongruent response, but more so among MCI patients. MCI patients taking a cholinesterase inhibitor showed smaller flanker interference effects than those not taking this medication. Analysis of the flanker effect as a function of the entire RT distribution indicated that MCI patients show increasing interference at the slowest segments of the distribution, a finding that implicates deficient inhibition of the incongruent response [Ridderinkhof, K. R. (2002). Activation and suppression in conflict tasks: Empirical clarification through distributional analyses. In W. Prinz & B. Hommel (Eds.), *Common mechanisms in perception and action. Attention & performance, Vol. XIX* (pp. 494–519). Oxford: Oxford University Press]. These results suggest that deficits in response inhibition are detectable in MCI patients and merit further investigation as to whether these changes aid prediction of which MCI patients convert to AD.

Keywords: MCI; Alzheimer’s disease; Executive; Flanker; Cognitive control; Memory

Alzheimer’s disease (AD) is a progressive neurodegenerative disease that targets brain regions known to play an essential role in the formation and consolidation of new memories. The vulnerability of regions within medial aspects of the temporal lobes, including the hippocampus and entorhinal cortex, is evident early in the course of AD and linked to the severity of memory decline (Jack, 2003; Petersen, 2000). Despite a primary emphasis on memory and related brain structures, investigations have increasingly focused on the compromise of other aspects of cognition that occur early in the course of AD. A growing literature implicates early and significant changes in executive cognitive abilities as well as early neurobiological changes in the frontal lobes (Baddeley, Baddeley, Bucks, & Wilcock, 2001; Baudic et al., 2006; Duke & Kasznia, 2000; Lafleche & Albert, 1995; Perry & Hodges, 1999; Royall, Palmer, Mulroy, & Polk, 2002; Swanberg, Tractenberg, Mols, Thal, & Cummings, 2004). As a result, frontal pathology and executive dysfunction have become important areas of investigation in contemporary AD research, especially at early stages of the disease.

The term mild cognitive impairment (MCI) describes a clinical condition in which an individual exhibits a decline in memory functioning that is greater than expected for age yet does not show the full range of cognitive deficits and impairments in activities of daily living that would warrant a diagnosis of AD (Chertkow, 2002; Petersen, 2000, 2004; Ritchie, Artero, & Touchon, 2001; Winblad et al., 2004). The utility of the MCI diagnosis is evidenced by consistent estimates that individuals with MCI are at greater risk for conversion to AD. Estimates vary, but individuals with MCI progress to AD at a rate of 10–25% per year as contrasted with healthy elderly controls who progress at a rate of 1–2% per year (Petersen et al., 2001; Petersen, 2004). Thus, MCI is thought to represent a pathologic
state and perhaps a transition stage into AD. As a result, most studies of MCI have focused on characterizing memory dysfunction and neuropathologic processes in brain areas linked to memory processes, e.g., hippocampus, (Petersen et al., 1999). Given the greater appreciation for decline in executive functions in the early stages of AD, the current study examines the presence of executive cognitive control deficits in MCI patients. By the term executive cognitive control, we refer to a set of emergent properties established by the configuration and tailoring of more basic mental functions so as to orchestrate and regulate behavior in accordance with internal goals and external demands. The detection of executive cognitive control deficits in MCI has the potential to inform the course of treatment and offer clues about the neuropathology and course of cognitive decline at an earlier point in the AD process.

Several existing lines of research support a potential link between MCI and executive dysfunction. For example, conjoining performance on clinical measures of executive cognitive abilities with memory performance has discriminated MCI patients from healthy elderly adults and improved prediction of MCI conversion to AD (Albert, Moss, Tanz, & Jones, 2001; Arnaiz, & Almkvist, 2003; Backman, Jones, Berger, Laukka, & Small, 2005; Chen et al., 2000, 2001; Crowell, Luis, Vanderploeg, Schinka, & Mullan, 2002; Rapp & Reischies, 2005; van der Flier et al., 2002). At least three longitudinal studies have demonstrated that abnormalities of the anterior cingulate cortex, a frontal lobe structure tied to several putative executive control processes, make a significant contribution to the prediction of MCI conversion to AD (Chetelat & Baron, 2003; Mosconi et al., 2004; van der Flier et al., 2002). A recent functional brain imaging study of MCI patients found complex attentional deficits in the context of reduced frontal lobe activation compared to healthy controls (Dannhauser et al., 2005). In studies of AD, strong ties between executive dysfunction and declines in functional activities of daily living have been reported (ADL) (Back-Madruza et al., 2002; Boyle et al., 2003; Earnst et al., 2001; Perry & Hodges, 1999), and a similar pattern has recently been reported in studies of MCI patients (Cahn-Weiner, Malloy, Boyle, Marran, & Salloway, 2000; Griffith et al., 2003; Tabert et al., 2002). Finally, and significant from a clinical perspective, caregivers of MCI patients observe an appreciable increase in executive dysfunction in everyday situations beginning with the onset of MCI symptoms (Ready, Ott, Grace, & Cahn-Weiner, 2003).

We add to this emerging literature by investigating an essential component of executive cognitive control, the inhibition of errant response tendencies, in a group of MCI patients whose primary deficit based on formal neuropsychological testing and neurological examination is memory. Response inhibition is critical when one must prevent the selection of a more automatic or prepotent course of action in favor of an alternative course of action (Nigg, 2001). Deficits of response inhibition often delay the selection of a desired action and increase the likelihood of responding in error. In AD, response inhibition deficits have been measured at early stages of the disease, and in a comprehensive review of this work, Amieva, Phillips, Della Sala, and Henry (2004) concluded that a deficit in controlled inhibitory skills is a robust and pervasive feature of AD (Amieva et al., 2002; Binetti et al., 1996; Bondi et al., 2002; Collette, van der Linden, Delrue, & Salmon, 2002; Fisher, Freed, & Corkin, 1990; Koss, Ober, Delis, & Friedland, 1984; Perry, Watson, & Hodges, 2000; Spieler, Balota, & Fausy, 1996). Thus, there is clear impetus for studying response inhibition deficits in individuals at risk for AD.

In the current study, we used a variant of the Eriksen flanker task (Eriksen & Eriksen, 1974) to induce response conflict and study the efficiency of response inhibition engaged to resolve this conflict. Participants made left or right manual responses to the direction of a target arrow (i.e., left pointing arrow = left manual response) that was flanked on each side by distractor arrows, or flankers. For trials void of response conflict, target and flankers pointed in the same direction and corresponded to the same manual response (i.e., flankers signaled a congruent response). For response conflict trials, target and flankers pointed in opposite directions, thus corresponding to opposite manual responses (i.e., flankers signaled an incongruent response). Consistent with an extensive literature on flanker effects, we predicted that reaction time (RT) and error rates would reliably increase in conflict trials compared to non-conflict trials (i.e., flanker effect) for MCI patients and healthy controls. We also predicted that the flanker effect would be larger in MCI patients, suggesting a disadvantage in resolving the response interference induced by the incongruent flankers.

According to most accounts, the flanker effect is largely determined by the strength of response activation induced by the flankers (i.e., stronger activation leads to greater interference) as well as how efficiently this activation can be inhibited (i.e., stronger inhibition reduces interference). By activation, we refer to the build up of neural activity over motor cortex toward a critical threshold that leads to generation of a corticospinal signal that executes the response. Dual processing conceptualizations capture these dynamics by positing that target and flankers are processed in parallel along two routes, a deliberate and a direct route (e.g., Kornblum, Hashbroucq, & Osman, 1990; Ridderinkhof, van der Molen, & Bashore, 1995). The target, by virtue of representing the imperative stimulus upon which a response is based, dominates processing along a slower, more deliberate stimulus–response translation route (i.e., the deliberate route) so as to ensure correct response selection. The direct route describes a fast, automatic activation of responses associated with the target and flankers, with the degree of activation closely related to the strength of the stimulus–response (S–R) association. Thus, over-learned or spatially compatible S–R associations trigger stronger direct response activation. In the flanker task, the visual array consists of multiple flankers and a single target. As a result, direct response activation is greater for the response signaled by the flankers, and this finding has been confirmed in several psychophysiological investigations that show stronger and earlier activation over motor cortex contralateral to the response hand signaled by the flankers (Bashore, 1990). The direct and deliberate routes converge at the level of response activation, and conflict arises when the flanker-dominated direct route activates an incongruent response. The inhibition of this direct activation, which helps to resolve the
conflict between the two routes in favor of the deliberate route, is a time-consuming operation that contributes to much of the slowing of overall RT (i.e., the flanker effect).

Because we are predicting larger flanker interference effects among MCI patients, it would be especially informative to determine if this change in MCI arises from stronger activation of the response triggered by the irrelevant flankers, inefficient inhibition of this activation, or contributions from both processes. Unfortunately, it is difficult to distinguish these processes using standard analyses of central tendency as a slowing of mean RT in the incongruent flanker condition merely indicates the degree of interference induced by the conflict. Recently, a model was introduced that combines principles of the dual processing model with distributional analytical techniques (i.e., delta plots, which plot the flanker interference effect as a function of RT), to distinguish the activation and subsequent inhibition of the response signaled by the flankers. According to the activation-suppression hypothesis, the activation of the target response as well as the activation and subsequent suppression (i.e., inhibition) of the flanker response correspond to unique onset times, accrual rates, and strengths that vary on a trial-by-trial basis (Ridderinkhof, 2002). As a result, the expression of these processes depends on the speed of a response, highlighting the importance of analyzing flanker effects as a function of the entire RT distribution.

One premise of the activation-suppression hypothesis proposes that group differences in the pattern of fast response errors can be used to infer the strength of response activation along the flanker-dominated direct route. This premise is largely based on the well known finding from event-related brain potential studies that the incongruent response signaled by the flankers is activated over motor cortex before the response signaled by the target is activated (Bashore, 1990). Both activations are thought to build toward a hypothetical response threshold that, if exceeded, engages the corresponding motor response. With stronger direct route activation of the incongruent response, one is more likely to reach the critical response threshold and commit a response selection error. This is especially true for fast reactions (relative to slower trials in a RT distribution) because response activation along the deliberate route continues to lag behind and inhibition has not had enough time to build an effective counter to the response activation along the direct route. The vulnerability of fast responses to incorrect response activation in the Eriksen flanker task has been demonstrated repeatedly using conditional accuracy functions (e.g., Gratton et al., 1992). Thus, higher error rates at the fastest segments of the RT distribution are suggestive of stronger direct response activation induced by flankers (Fig. 1).

Whereas the patterns of error rates can be used to infer the strength of response activation induced by the flankers, it is important to point out that in the vast majority of studies most trials containing incongruent flankers are performed accurately. While stronger direct response activation might increase the likelihood of committing a response error, most of the time this activation is successfully inhibited from reaching the critical response threshold. Thus, a consideration of the temporal characteristics of the direct and deliberate processing routes for accuracy incongruent flanker trials generates important predictions concerning the role of inhibition. If response activation along the deliberate route proceeds quickly, then the incorrect response activation along the flanker-dominated direct route has less time to “build up”, and the likely result is a fast, accurate response with minimal interference from the direct route (i.e., smaller flanker effects on RT). If response activation generated along the deliberate route is slow, more time is available for the “build up” of response activation along the direct route, and the likely result is a slow, accurate response due to greater interference from the direct route (i.e., larger flanker effects). Thus, for accurate responses, the dual processing route conceptualization predicts that flanker interference effects on RT should tend to increase from the fastest to the slowest segments of the RT distribution.

However, the activation-suppression hypothesis predicts a different pattern based on the role of inhibition. The resolution of response interference depends in large part on the selective suppression (or inhibition) of the response activation along the direct route (i.e., the incongruent response), and this selective inhibition process can also vary in effectiveness on a trial-by-trial basis. Because the onset of inhibition occurs after direct route activation and takes time to build-up (cf. Eimer & Schlaghecken, 1998), the effects of inhibition should be revealed most prominently at slower segments of the RT distribution. If net inhibition is efficient (i.e., is strong or builds up quickly), the flanker interference effect should taper at slower segments of the RT distribution. If net inhibition is inefficient (i.e., is weak or builds up slowly), the flanker interference effect should continue to increase at a steeper rate or taper at later segments of the RT distribution compared to efficient inhibition. Thus, across the entire RT distribution, the magnitude of the flanker interference effect is predicted to rise across early segments of the distribution, but taper at the slower segments (with effective inhibition).1

As a reviewer pointed out, other accounts have also predicted a linear increase in flanker effects across the RT distribution. For example, De Jong, Berendse, & Cools et al. (1999) predicted that larger interference effects at the slowest segment of the RT distribution reflect different levels of response interference.
Based on this reasoning, group differences in the efficiency of inhibition are expected to emerge at slower segments of the RT distribution, with more efficient inhibition associated with a greater tapering of the flanker interference effect and inefficient inhibition associated with less tapering of the flanker interference effect (Fig. 2).

The patterns predicted by the activation–suppression hypothesis have been supported in several experiments using the flanker task as well as in tasks that similarly induce response conflict (e.g., Simon and Stroop tasks; Bub, Masson, & Lalonde, 2006; Burle, Possamaï, Vidal, Bonnet, & Hasbroucq, 2002). Studies of individual differences also support the predicted patterns of RT and accuracy, but have also been helpful for distinguishing the unique roles of response activation and inhibition in accounting for abnormal flanker effects. For example, larger flanker effects in children with attention-deficit hyperactivity disorder (ADHD) compared to healthy control children were shown to result from less efficient inhibition rather than stronger activation of incongruent responses (Ridderinkhof, Scheres, Oosterlaan, & Sergeant, 2005). This pattern was revealed by a divergence between the flanker effects at the slower segments of the RT distribution, a finding consistent with inefficient inhibition.

In the current study, we apply the reasoning of the activation–suppression hypothesis, first asking if MCI patients show greater interference in the context of response conflict (i.e., larger overall flanker interference effects), and then analyzing the distributional pattern of flanker effects to determine if MCI patients experience stronger activation and/or inefficient inhibition of a conflicting response.

### Table 1

<table>
<thead>
<tr>
<th></th>
<th>HC</th>
<th>MCI</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sample size</td>
<td>20</td>
<td>20</td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>71.5 (8.7)</td>
<td>73.0 (6.1)</td>
<td>n.s.</td>
</tr>
<tr>
<td>Education (years)</td>
<td>16.0 (2.6)</td>
<td>15.6 (2.7)</td>
<td>n.s.</td>
</tr>
<tr>
<td>Gender (M:F)</td>
<td>9:11</td>
<td>8:12</td>
<td></td>
</tr>
<tr>
<td>Depression rating (CES-D)</td>
<td>9.2 (8.8)</td>
<td>12.7 (8.8)</td>
<td>n.s.</td>
</tr>
<tr>
<td>AMNART (estimated IQ)</td>
<td>121.5 (7.3)</td>
<td>118.5 (8.2)</td>
<td>n.s.</td>
</tr>
<tr>
<td>MMSE (raw score)</td>
<td>29.3 (0.8)</td>
<td>26.0 (2.5)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CVLT (total words)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Short delay free recall</td>
<td>10.5 (3.5)</td>
<td>2.6 (2.6)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Long delay free recall</td>
<td>10.7 (3.2)</td>
<td>2.5 (3.0)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Stroop interference [C−CW/C]</td>
<td>0.47 (0.1)</td>
<td>0.48 (0.1)</td>
<td>n.s.</td>
</tr>
<tr>
<td>RBANS (raw scores)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Picture copy</td>
<td>17.6 (2.0)</td>
<td>17.4 (2.5)</td>
<td>n.s.</td>
</tr>
<tr>
<td>Picture recall</td>
<td>14.3 (2.2)</td>
<td>3.2 (3.9)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Object naming</td>
<td>9.9 (0.2)</td>
<td>9.7 (0.5)</td>
<td>n.s.</td>
</tr>
<tr>
<td>Semantic fluency</td>
<td>21.5 (6.0)</td>
<td>16.2 (4.6)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Flanker task</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neutral (NT) RT (ms)</td>
<td>479 (63)</td>
<td>505 (64)</td>
<td></td>
</tr>
<tr>
<td>Accuracy (%)</td>
<td>99.8 (0.3)</td>
<td>99.4 (1.0)</td>
<td></td>
</tr>
<tr>
<td>Congruent (CG) RT (ms)</td>
<td>486 (68)</td>
<td>517 (74)</td>
<td></td>
</tr>
<tr>
<td>Accuracy (%)</td>
<td>99.8 (0.3)</td>
<td>99.5 (0.9)</td>
<td></td>
</tr>
<tr>
<td>Incongruent (IG) RT (ms)</td>
<td>557 (80)</td>
<td>612 (86)</td>
<td></td>
</tr>
<tr>
<td>Accuracy (%)</td>
<td>98.0 (3.0)</td>
<td>97.3 (3.4)</td>
<td></td>
</tr>
<tr>
<td>Flanker effect (IG–CG) RT (ms)</td>
<td>71 (24)</td>
<td>94 (34)</td>
<td></td>
</tr>
<tr>
<td>Accuracy (%)</td>
<td>−1.7 (2.9)</td>
<td>−2.1 (3.1)</td>
<td></td>
</tr>
<tr>
<td>Delta values (IG–CG) Quintile 1 RT (ms)</td>
<td>43 (25)</td>
<td>46 (26)</td>
<td></td>
</tr>
<tr>
<td>Accuracy (%)</td>
<td>−6.2 (13.8)</td>
<td>−6.1 (10.8)</td>
<td></td>
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<tr>
<td>Quintile 2 RT (ms)</td>
<td>58 (21)</td>
<td>66 (28)</td>
<td></td>
</tr>
<tr>
<td>Accuracy (%)</td>
<td>−1.7 (3.2)</td>
<td>−3.3 (6.0)</td>
<td></td>
</tr>
<tr>
<td>Quintile 3 RT (ms)</td>
<td>68 (26)</td>
<td>81 (33)</td>
<td></td>
</tr>
<tr>
<td>Accuracy (%)</td>
<td>−0.2 (1.0)</td>
<td>−0.2 (1.1)</td>
<td></td>
</tr>
<tr>
<td>Quintile 4 RT (ms)</td>
<td>78 (32)</td>
<td>97 (40)</td>
<td></td>
</tr>
<tr>
<td>Accuracy (%)</td>
<td>0.0 (0.0)</td>
<td>−0.2 (1.9)</td>
<td></td>
</tr>
<tr>
<td>Quintile 5 RT (ms)</td>
<td>97 (52)</td>
<td>170 (76)</td>
<td></td>
</tr>
<tr>
<td>Accuracy (%)</td>
<td>−0.7 (2.4)</td>
<td>−0.8 (4.2)</td>
<td></td>
</tr>
</tbody>
</table>

### 1. Methods

#### 1.1. Participants

Twenty individuals diagnosed with MCI and 20 healthy controls (HC) similar in age (p > 0.10) and education (p > 0.10) participated in this study (Table 1). The MCI participants were identified in the Memory Disorders Clinic at the University of Virginia based on the following criteria: subjective memory complaint, objective memory impairment relative to baseline abilities determined by formal neuropsychological testing, the absence of appreciable impairment in other cognitive domains based on formal neuropsychological testing, the absence of...
appreciable impact of memory deficits on activities of daily living, a neuro-
logical examination that included brain imaging data to rule out other possible
sources of cognitive impairment (e.g., stroke, epilepsy, infection), and a consen-
sus diagnosis of MCI made by a neurologist and two neuropsychologists. None
of the MCI patients met NINDS-ADRDA criteria for a diagnosis of AD. Some
of the HC participants were spouses or family members of MCI patients, but
most were recruited in the local community via advertisement.

Twelve MCI patients were taking medication (e.g., cholinesterase inhibitors)
designed to slow the progression of cognitive decline, nine patients were
stable on pharmacotherapy to treat depression (selective serotonin reuptake
inhibitor = 7; serotonin agonist = 1, benzodiazepine for anxious depression = 1),
and three patients were taking both of the latter medications. Two participants
from the HC group were stable on anti-depressant pharma-
cotherapy (both taking an SSRI). Exclusion criteria included the following:
history of neurological insult or stroke; untreated or unstable mood disor-
der, including depression; history of bipolar affective disorder, schizophrenia,
or other psychiatric conditions known to compromise cognitive functioning;
untreated or unstable medical conditions known to interfere with cognitive func-
tioning (e.g., diabetes, pulmonary disease). All participants provided informed
consent prior to inclusion into the study, which was approved by the human
investigation committee at the University of Virginia Health Systems.

1.2. Tasks and procedures

In addition to performing the flanker task (described below), each participant
completed a measure of depression (Center for Epidemiologic Studies Depres-
sion Scale, CES-D; Radloff, 1977) and a battery of paper-and-pencil tasks to
assess baseline cognitive functioning and confirm the primary memory deficit
in MCI patients. The cognitive battery included measures of estimated verbal
IQ (AMNART; Blair & Spreen, 1989), global mental status (MMSE; Folstein,
Folstein, & McHugh, 1975), word list learning and memory (California Verbal
Learning Test—second edition (CVLT); Delis, Kramer, Kaplan, & Ober, 1987),
subtests from the Repeatable Battery for the Assessment of Neuropsychological
Status (RBANS; Randolph, 1998) that encompassed visuoconstruction, visual
memory, picture naming, and word fluency, and a measure of response inter-
ference using a clinical version of the Stroop Color-Word Test (Goldstone, 1978),
which individually measures word-reading (W), color-naming (C), and color-
word naming (CW) performance in 45 s. An interference score from the Stroop
Color-Word Test was calculated by the ratio, [I – (C – CW)/C], which corrects for
color naming speed and controls for lexical and motor output processes (Bondi
et al., 2002; Taylor, Kornblum, Lauber, Minoshima, & Koeppe, 1997). The order
of task completion was fixed to facilitate the delays required for the memory
recall portions of the CVLT and the memory subtests of the RBANS.

The flanker task was programmed using E-prime software (www.pstnet.com;
Psychology Software Tools, Inc.) and implemented on an IBM-compatible com-
puter with a 17-in. digital display computer screen. The computer screen was
placed at a distance of 91 cm and positioned so that stimuli appeared at eye level.
Stimuli consisted of white arrows (pointing in the left or right direction) or white
diamonds against a black background. Responses to stimuli were registered via
a button box designed to interface with E-prime software. Participants held the
button box so that the right and left thumbs rested comfortably on corresponding
right and left response buttons.

Each trial began with the presentation of a fixation cross in the center of the
color display screen. After 500 milliseconds (ms), the cross was extinguished and
replaced by a stimulus array that remained on the screen until the participant
made a response. Each array consisted of 5 stimuli, a target arrow located in
the same center location as the fixation cross, and two distractor stimuli (i.e.,
flankers) located on each side of the target arrow. The entire array spanned
22.5 cm (visual angle = 14°), and each arrow measured 3.5 cm in height and
4.0 cm in width (visual angle = 2.5°). Participants were instructed to make a
button press based on the direction of the target arrow (e.g., right pointing
arrow = right button press; left pointing arrow = left button press) and to ignore
flankers. After a response, the stimulus array disappeared and the screen
remained blank for 750 ms until a fixation cross appeared and signaled the
beginning of a new trial.

Each trial was defined by the configuration of flankers that surrounded the
target. In Neutral stimulus arrays, the flankers consisted of diamond shapes
that did not specify a particular response (◇◇→◇◇). For Congruent
stimulus arrays, flankers consisted of arrows pointing in the same direction
as the target arrow, thus corresponding to the same response as the target
(→→→→→→). For Incongruent stimulus arrays, flankers arrows pointed in
the opposite direction of the target arrow and corresponded to the conflicting manual
response (←←←←←←). Each flanker condition (neutral, congruent, incongruent)
appeared randomly and with equiprobability in a block of trials. Every
participant completed a block of 30 practice trials followed by three experimental
blocks, each of which contained 103 trials, for a total of 309 experimental trials.

Reaction times (RT) and accuracy rates were the primary dependent variables
of interest. For each subject, extreme RT values (i.e., greater than 3 standard
deviations above the mean) in each condition were discarded, accounting for
fewer than 2% of trials per flanker condition per subject. Visual inspection of
discarded trials confirmed that only extreme, outlying values were eliminated
from analysis. RT and accuracy data were analyzed in two ways. First, RTs
(for correct responses only) and accuracy rates were submitted to an overall
mean analysis (repeated-measures ANOVA with Huynh-Feldt corrections for
violations of sphericity) to determine the effects of Flanker Condition (neu-
tral, congruent, incongruent) and Group (MCI, HC). This is the conventional
method for determining the interference effect due to incongruent flankers. The
second approach considered the flanker effect as a function of the RT distribu-
tion and followed procedures similar to Ridderinkhof (2002) and Ridderinkhof
et al. (2005). For each participant, RTs for all responses in each flanker condi-
tion were ranked ordered and partitioned into 5 equal size bins (quintiles, Q1–Q5).
Next, mean RT and accuracy rates were calculated for each quintile, Five flanker
effect sizes (delta values) were generated by subtracting mean RT and accuracy
rates for the congruent condition from the incongruent condition for each quin-
tile. Delta plots for RT and accuracy were then constructed by plotting delta
values as a function of average RT for each quintile. The slopes between each
quintile (e.g., Q1–Q2, Q2–Q3, Q3–Q4, Q4–Q5) from the RT delta plot and the
slope between the first and second quintile from the accuracy delta plot were
submitted to separate ANOVA to determine the effect of Group (MCI, HEC).
Analysis of slopes as opposed to raw delta values accommodates the standard
statistical property of RT distributions that the variance increases with the mean
(Wagenmakers, Grasman, & Molenaar, 2005).

2. Results

2.1. Baseline cognitive and emotional measures

Table 1 displays the mean values for each of the cognitive
and emotional measures completed by MCI patients and
healthy controls. The MCI and HC groups did not differ on clinical
measures of verbal intelligence, visuospatial organization and
construction, a clinical measure of response interference
(Stroop Color-Word Test), or an important aspect of language
functioning, object naming (all p > 0.10). Consistent with the
MCI diagnosis, the primary difference between the groups was
found on measures of short delay verbal memory [CVLT short
delay free recall: F(1, 38) = 63.44, p < 0.001], long delay ver-
bal memory [CVLT long delay free recall: F(1, 38) = 69.76,
p < 0.001], and delayed visual memory [RBANS picture recall;
F(1, 38) = 118.38, p < 0.001]. Notably, the groups also differed on
a measure of semantic word fluency, with MCI patients gener-
ergating fewer words related to the category “animals” over the
span of one minute [F(1, 38) = 9.79, p < 0.01]. The MCI and HC
groups did not differ on a self-report measure of depression,
[F(1, 38) = 1.56, p = 0.21].

2.2. Flanker task

2.2.1. Mean analysis of the flanker effect

Overall analysis of mean RT showed a significant flanker
effect, [F(1,4, 56.2) = 262.16, p < 0.001]. For both groups, incon-
gruent flankers produced a significant slowing of RT compared to neutral and congruent flankers (Fig. 3). Overall RT was slower in MCI patients (544 ms) than in HC subjects (507 ms), although this difference was not statistically reliable \(F(1, 38) = 2.79, p = 0.10\). Importantly, the Group × Flanker interaction was significant, \(F(1.4, 56.2) = 5.72, p = 0.01\); compared to the HC group, the MCI patients showed a larger RT cost (71 ms versus 95 ms for HC and MCI groups, respectively) in the incongruent condition compared to the congruent condition. Baseline average RT (using the neutral flanker condition) did not correlate with the magnitude of the flanker effect (computed as the RT difference between incongruent and congruent conditions) in MCI \((r = 0.19, p = 0.40)\) or HC \((r = 0.34, p = 0.13)\) groups. There were no group differences in overall accuracy rates \(F(1, 38) = 1.13, p = 0.29\), but there was a significant effect of flanker condition on accuracy, \(F(1.1, 43.6) = 17.17, p < 0.001\). Incongruent flankers reduced accuracy in both groups compared to neutral and congruent flankers, but this effect did not differ by group \(\text{Group} \times \text{Flanker interaction}, F(1.1, 43.6) = 0.15, p = 0.73\) (Table 1).

2.2.2. Distributional analysis of the flanker effect

To investigate the distributional characteristics of the flanker effect, we submitted the slopes of the RT delta plot between successive quintiles and the slope between the first two quintiles for the accuracy delta plot function to separate repeated-measures ANOVA. An analysis of slopes is important as the analysis of mean delta values does not accommodate for the disproportional increase in RT across slower segments of the distribution or for group differences in the variability of RT at the slowest segments.

The results from the analysis of slopes of the RT delta plot showed a significant group effect \(F(1, 38) = 3.83, p = 0.05\); the overall increase in delta plot slope was greater for MCI (slope = 0.37) patients than for HC (slope = 0.24). However, there was no main effect of slope across quintiles \(F(3, 114) = 0.86, p = 0.46\). The analysis also showed a significant Slope × Group interaction \(F(3, 114) = 2.59, p = 0.05\). Visual inspection of Fig. 4 shows that group delta plot slopes diverge between the last two segments of the distribution, with an increase in the delta slope among MCI patients and a tapering of the slope among HC participants. Statistically, delta plot slopes did not differ between groups at the fastest segments, \(Q1–Q2: F(1, 38) = 0.02, p = 0.87; Q2–Q3: F(1, 38) = 0.86, p = 0.36; Q3–Q4: F(1, 38) = 1.06, p = 0.30\), but were reliably different at the slowest segment of the distribution, \(F(1, 38) = 9.36, p < 0.01\), confirming the visual observations from Fig. 4. According to the activation–suppression hypothesis, group differences in response activation are revealed in the pattern of response errors at the fastest segments of the distribution. As can be observed in Fig. 5, the majority of errors were confined to the fastest segment of the distribution in both groups and accuracy differences between congruent and incongruent trials approached zero after the second quintile. Thus, we were only interested in determining group differences in the slope of the accuracy delta plot between the first two segments of the distribution. A simple contrast between these segments \(Q1–Q2\) showed that the delta plot accuracy slope did not differ between groups, \(F(1, 38) = 0.32, p = 0.57\).
2.2.3. The effects of pharmacotherapy on flanker interference in MCI

To explore the possible role of pharmacotherapy treatment on flanker interference effects in the MCI group, we submitted mean RTs to separate repeated-measures ANOVA for subgroups of MCI patients based on anti-depressant treatment and cholinesterase inhibition treatment. First, we partitioned the MCI group into two groups based on whether the participant was stable on anti-depressant medication (n = 9) or not taking anti-depressant medication (n = 11). The depression treatment subgroup (mean age = 69.7) was slightly younger than the no depression treatment subgroup (mean age = 75.6), [F(1, 18) = 5.48, p = 0.03], but the groups did not differ on any of the background or baseline cognitive measures (all p > 0.10). Importantly, the groups did not differ on a self-report measure of depression (CES-D), [F(1, 18) = 0.06, p = 0.79]. The mean RT analysis revealed a significant Flanker effect, [F(1.6, 29.8) = 127.18, p < 0.001]; both groups showed slower RTs in the incongruent flanker condition compared to the neutral and congruent flanker conditions. The main effect of group was insignificant, [F(1, 18) = 0.02, p = 0.88], and there was no Group × Flanker interaction, [F(1.6, 29.8) = 0.36, p = 0.65].

Fig. 6 (upper panel) depicts the strikingly similar pattern of RT effects under each flanker condition for the two groups partitioned according to depression treatment.

A second analysis compared patients on cholinesterase inhibition medication (n = 12) to those not taking this medication (n = 8). The groups did not differ in age, education, or performance on any of the baseline cognitive or emotional measures (all p > 0.10). The groups also did not differ in terms of overall RT, [Group effect: F(1, 18) = 0.002, p = 0.96]. As expected, both groups showed a significant Flanker effect, [F(1.8, 32.4) = 164.04, p < 0.001], with RT significantly slowed in the incongruent flanker condition compared to the neutral and congruent conditions. However, the Group × Flanker interaction was significant, [F(1.8, 32.4) = 4.99, p = 0.01]. As Fig. 6 (lower panel) depicts, the subgroup of MCI patients taking cholinesterase inhibition medication showed a smaller flanker interference effect compared to the group of MCI patients not receiving cholinesterase inhibition pharmacotherapy.

To determine if the cholinesterase inhibition medication effect could be attributed to response activation and/or inhibition, we looked at the distribution of the flanker effect as a function of RT. Fig. 7 (upper panel) displays the accuracy delta plot for the subgroups of MCI patients taking and not taking cholinesterase inhibition pharmacotherapy. A simple contrast between the first fastest segments (Q1–Q2) showed that the delta plot accuracy slope did not differ between groups, F(1,
ally tapered to a larger extent compared to MCI, suggesting that the RT distribution, presumably when inhibition is engaged and magnitude of the flanker effect diverged at slowest segments of the distribution. However, the delta values representing the activation signaled by the incongruent response did not differ between the groups. Thus, these patterns suggest that cholinesterase inhibition pharmacotherapy may alter the efficiency of response inhibition as opposed to response activation.

3. Discussion

The primary aim of this study was two-fold: (1) to determine if individuals with MCI have greater difficulty resolving response conflict than healthy elderly controls, and (2) to determine if MCI patients experience stronger activation or poorer inhibition of a conflicting response. To the best of our knowledge, we report the first data on the performance of MCI patients using the flanker task. Both HC and MCI groups showed a significant RT cost when responding to a target stimulus that was surrounded by distractors that signaled a conflicting response, and as predicted, this RT cost was larger among MCI patients. Moreover, analysis of the flanker interference effect as a function of the entire RT distribution suggested that inefficient inhibition rather than greater activation of the response induced by incongruent flankers accounted for the enhanced interference effect in MCI patients.

Our findings support the utility of distributional analyses as a convenient tool for investigating the underlying processes (e.g., activation, inhibition) that contribute to group and individual differences in interference effects. According to the activation–suppression hypothesis, differences in response activation should be revealed at the fastest segments of the RT distribution in the percentage of fast errors, with stronger activation corresponding to more frequent fast errors. In contrast, differences in the efficiency of selective inhibition should emerge at slower segments of the RT distribution as inhibition is engaged to counter the build-up of response activation along the direct route. According to the model, the expected increase in the flanker effect across the distribution should taper with efficient inhibition. Minimal change in the rise of the flanker effect across the RT distribution is expected with weaker, inefficient inhibition.

Differences between MCI and HC groups in the flanker effect, assessed by RT and accuracy, did not exist at the fastest segments of the RT distribution, suggesting that the level of response activation signaled by the incongruent response did not differ between the groups. However, the delta values representing the magnitude of the flanker effect diverged at slowest segments of the RT distribution, presumably when inhibition is engaged and building up to counter direct route activation. In the HC group, the increase in the flanker effect across the distribution eventually tapered to a larger extent compared to MCI, suggesting that the HC group engaged more effective inhibition. In MCI, the flanker effect continued to increase over the distribution, consistent with less efficient inhibition of the incongruent response activated along the direct route.

A potentially important observation was made when we evaluated the flanker interference effect in subgroups of MCI patients who were stable on cholinesterase inhibition pharmacotherapy and those who were not taking this medication. Whereas cholinesterase inhibitors are used most commonly in AD to slow the progression of memory decline, there is increasing interest in the effects of this medication on cognitive functioning in MCI (Goekoop et al., 2004; Koontz & Baskys, 2005). Although we did not directly measure the effects of cholinesterase inhibition in MCI patients, cholinesterase inhibition is known to modulate frontal lobe activity (Thiel, 2003). In our study, the flanker interference effect was smaller among patients stable on cholinesterase inhibition pharmacotherapy compared to those not taking this medication. Furthermore, differences in the distributional analyses emerged at slower segments of the RT delta plot, a finding that suggests less efficient inhibition in patients not taking cholinesterase inhibition medication compared to those taking this medication. These findings are similar to Saykin et al. (2004), who found that cholinesterase inhibition enhances frontal circuitry activity and executive cognitive performance in some patients with MCI. Similar effects have also been demonstrated in studies of AD (Foldi, White, & Schaefer, 2005; Kaasinen et al., 2002; Mega et al., 2005; Rombouts, Barkhof, van Meel, & Scheltens, 2002). While in need of more focused study and replication, this suggests that cholinesterase inhibition may have important beneficial effects on cognitive control processes that resolve response conflict. Future studies in MCI that measure response inhibition before and during cholinesterase inhibition pharmacotherapy may be particularly informative to neurocognitive models of treatment effects as well as neurocognitive models of response inhibition.

Inefficient response inhibition adds to a limited, but emerging, literature that shows selective deficits in executive cognitive skills in MCI patients who do not yet meet criteria for AD. In a recent example, MCI patients had greater difficulty (i.e., longer RT) resolving expectancy violations in a semantic priming task (Davie et al., 2004). The authors proposed that MCI patients may be less effective at suppressing the automatic activation of semantic representations. A study by Rosano et al. (2004) did not show greater RT or accuracy costs among MCI patients compared to healthy controls when making incompatible responses (e.g., a right button press to a left pointing arrow), which requires suppression of the more automatic, compatible response tendency (e.g., a left button press to a left pointing arrow). However, compared to healthy controls, MCI patients showed greater activation in posterior parietal cortex and weaker dorsolateral prefrontal cortex activation during incompatible response conditions. While the former was consistent with compensatory activation, the latter was postulated to reflect compromised frontal lobe functioning supporting executive cognitive control processes. Thus, the results from these studies along with the current findings suggest that the capacity for inhibiting prepotent response tendencies may be vulnerable in...
MCI patients. Importantly, these findings are consistent with deficits in response inhibition that have been demonstrated in mild AD patients using several measures of response inhibition (for review, see Amieva et al., 2004; Perry & Hodges, 1999), although we are not aware of studies using the flanker task. The Stroop effect has most often been used to study response inhibition in mild AD, and while this effect undoubtedly measures more than response inhibition (i.e., unlikely a “pure” measure of inhibition), a review of several studies indicates that mild AD patients have larger Stroop effects than age-matched healthy controls (Amieva et al., 2004). Thus, response inhibitory deficits occur at the earliest stages of AD, and the current findings extend and add further precision to this work by suggesting that a diagnosis of MCI, which is believed to represent a transitional stage between normal aging and AD, is also associated with deficits of response inhibition. Whether early changes in response inhibition in MCI patients are predictive of who will convert to AD is an interesting question for future studies.

Several lines of evidence argue for an essential role of frontal-basal ganglia circuits in mediating response inhibition (Band & van Boxtel, 1999), and imaging studies of the flanker effect demonstrate activations in areas associated with these circuits. Specifically, dorsolateral prefrontal cortex, anterior cingulate cortex (ACC), the inferior frontal lobes, and the caudate nucleus are differentially active during incongruent flanker conditions compared to congruent flanker conditions (Botvinick, Nystrom, Fissell, Carter, & Cohen, 1999; Casey et al., 2000; Hazeltine, Poldrack, & Gabrieli, 2000; Lau, Rogers, & Passingham, 2006; Rafal et al., 1996; Ro, Cohen, Ivry, & Rafal, 1998). Moreover, individuals suffering disease that disrupts the integrity of these brain areas (e.g., Parkinson’s disease) also show larger flanker interference effects compared to healthy controls (Praamstra Stegeman, Cools, & Horstink, 1998; Praamstra, Plat, Meyer, & Horstink, 1999; Wylie, Stout, & Bashore, 2005). The link to MCI pathology is indirect, but as pointed out earlier, recent studies have suggested that dysfunction of ACC increases prediction of MCI conversion to AD (Chetelat & Baron, 2003; Mosconi et al., 2004; van der Flier et al., 2002). Given the strong involvement of ACC activation during response conflict trials of the flanker task, it is interesting to speculate that the declines in response inhibition in MCI measured in the current study may be related to ACC dysfunction (Ridderinkhof, Ullsperger, Crone, & Nieuwenhuis, 2004). We are currently testing this possibility by analyzing the relationship between the magnitude of flanker effects and neurochemical abnormalities (using magnetic resonance spectroscopy) in the ACC.

Our results highlight the issue of task sensitivity in detecting executive cognitive control deficits in MCI patients. In the present study, detection of response inhibition deficits in MCI required the use of an experimental cognitive measure (the flanker task) as MCI and HC groups did not differ on a widely used clinical version of the Stroop Interference effect (Table 1). The differential sensitivity may result from a few sources, including the temporal nature of the task as well as the analysis technique. Like many clinical measures of executive functioning, the version of the Stroop task we used measures performance over a longer period of time (several seconds) rather than on a trial-by-trial basis as measured by the flanker task. Thus, response inhibitory differences may be best captured using instruments that are temporally more sensitive and precise. In terms of the analysis issue, we note that group differences also emerged on the flanker task when we took into consideration the distributional properties of performance, which is seldom the case when conventional neuropsychological measures are analyzed.

A few caveats concerning the present study are worth discussing. One of the challenges in this line of research is the definition of MCI. Debate continues regarding the most useful way to operationalize the MCI diagnosis, although most classification systems require a subjective memory complaint, informant (e.g., family, caretaker) corroboration of memory difficulty, relatively intact activities of daily living, and normal or benign difficulties in non-memory aspects of cognition (Chertkow, 2002; Petersen, 2004). More stringent systems specify the degree of severity of memory impairment based on standardized neuropsychological tests (e.g., performance < 1.5 standard deviations below the mean), although there are limitations to this approach (Petersen, 2004). In our study, the diagnosis of MCI was based on the presence of focal memory impairment following neuropsychological and neurological evaluation, minimal cognitive declines in other domains, and the denial that memory deficits were disruptive to normal activities of daily living. Essentially, we wished to study individuals with the amnestic presentation of MCI who have a high risk of converting to AD (Petersen, 2004; Winblad et al., 2004). Our baseline cognitive measures confirmed the presence of primary memory impairment in the MCI group. Only one other area of cognitive functioning, fluent word generation, was different between the two groups, with MCI patients generating five fewer words over the span of a minute compared to the HC group. Deficits in word fluency have also been reported in other studies of MCI (Murphy, Rich, & Troyer, 2006; Ribeiro, de Mendonca, & Guerreiroa, 2006), but like these studies, the most striking difference between the groups in the current study was the degree of memory impairment. The MCI and HC groups did not differ on a clinical version of the Stroop Interference Task, suggesting that clinical measures of response inhibition may not always be sensitive enough to capture the subtleties of executive cognitive control deficits.

An important medication-related issue concerned the fact that nine of the MCI patients were stable on anti-depressant medication. However, this seems not to have been a significant factor in the current study. First, depression ratings did not differ between the subgroups of MCI patients taking and not taking anti-depressant medication. Second, our analysis of these subgroups showed no differences in flanker effects or overall RT. Lastly, the MCI group as a whole did not report higher levels of depression than the HC group. Despite the fact that depression and related treatment did not appear to play an important role in the current findings, the relationship between depression in MCI and deficits in executive cognitive control processes seems a related and important area for future investigation. Indeed, recent studies implicate an important relationship between depression and MCI (Geda et al., 2006).
Finally, RT studies of patient populations require consideration of the potential confounds of slowed processing speed and poor visual discriminability in accounting for effects. In this study, these influences unlikely affected the results. In the case of global processing speed, RT effects were isolated to the incongruent flanker condition, and neither group showed differential effects when comparing the neutral and congruent conditions. Furthermore, analysis of RT distributions showed that the flanker effects between the two groups were of similar magnitude at the earliest segments of the distribution and diverged at the segments theoretically linked to the process of response inhibition. The selectivity of RT and accuracy effects argues against a global slowing account. Further strengthening this point was the finding of no relationship between the magnitude of the flanker effect and baseline RT in the neutral flanker condition. Regarding visual deficits, it is notable that deficits in certain aspects of visual processing have been described in AD (Cormack, Tovee, & Ballard, 2000; Jackson & Owsley, 2003; Rizzo, Anderson, Dawson, & Nawrot, 2000). However, we do not think that altered visual processing played a significant role in the current study. All participants had normal or corrected-to-normal vision and performance on a measure of object recognition and design copy did not differ between MCI and HC groups, suggesting that visuospatial and visuospatial discrimination abilities were similar in both groups.

4. Conclusion

Individuals diagnosed with MCI show primary memory deficits and are at increased risk for developing AD. Recent studies show that individuals with AD display deficits in executive cognitive skills early in the course of the disease, raising important questions about the presence of similar deficits in individuals at-risk for AD. In this study, we show that MCI patients experience greater difficulty resolving the conflict created when distractors in the visual field activate a response that competes with a response signaled by a target stimulus. Importantly, the source of this difficulty appears to arise from inefficient response inhibition engaged to counter the activation of the competing response. Our findings also highlight the possibility that cholinesterase inhibition pharmacotherapy may be beneficial to resolving response conflict as patients taking this medication showed smaller flanker interference effects than those not taking the medication. The presence of response inhibition deficits in MCI patients adds to accruing evidence that certain aspects of executive cognitive control are compromised in this population and further strengthens the case for executive cognitive dysfunction as a potential precursor of AD.

Acknowledgment

This research was supported by the Virginia Institute on Aging at the University of Virginia. We would like to extend special thanks to Wery van den Wildenberg for helpful discussion and Victoria Powell for assistance in data collection.

References


