

## REVIEW ARTICLE

## Inhibitory functioning in Alzheimer's disease

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## Summary

We present a comprehensive review of studies assessing inhibitory functioning in Alzheimer's disease. The objectives of this review are: (i) to establish whether Alzheimer's disease affects all inhibitory mechanisms equally, and (ii) where possible, to assess whether any effects of Alzheimer's disease on inhibition tasks might be caused by other cognitive deficits, such as slowed processing. We review inhibitory mechanisms considered to play a crucial role in various domains of cognition, such as inhibition involved in working memory, selective attention and shifting abilities, and the inhibition of motor and verbal responses. It was found that whilst most inhibitory mechanisms are affected by the disorder, some are relatively preserved, suggesting that inhibitory deficits in Alzheimer's disease may not be the result of a general inhibitory breakdown. In particular, the experimental results reviewed showed that

Alzheimer's disease has a strong effect on tasks requiring controlled inhibition processes, such as the Stroop task. However, the presence of the disease appears to have relatively little effect on tasks requiring more automatic inhibition, such as the inhibition of return task. Thus, the distinction between automatic, reflexive inhibitory mechanisms and controlled inhibitory mechanisms may be critical when predicting the integrity of inhibitory mechanisms in Alzheimer's disease. Substantial effects of Alzheimer's disease on tasks such as negative priming, which are not cognitively complex but do require some degree of controlled inhibition, support this hypothesis. A meta-analytic review of seven studies on the Stroop paradigm revealed substantially larger effects of Alzheimer's disease on the inhibition condition relative to the baseline condition, suggesting that these deficits do not simply reflect general slowing.

**Key words:** inhibition; ageing; dementia; Alzheimer's disease**Abbreviations:** IOR = inhibition of return; NP = negative priming; RIF = retrieval-induced forgetting

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## Introduction

*Attentional deficits in Alzheimer's disease*

Episodic amnesia is often the earliest cognitive marker of Alzheimer's disease (e.g. Cummings and Benson, 1983; Petersen *et al.*, 1994; Linn *et al.*, 1995; Grober *et al.*, 1999; Perry *et al.*, 2000; Schmand *et al.*, 2000). There is considerable evidence that attentional and executive deficits are also an important feature of the cognitive deterioration in Alzheimer's disease (Spinnler, 1991; Balota and Faust, 2001; Della Sala and Logie, 2001), and that these deficits typically occur early in the disease (Foldi *et al.*, 2002) and may be the first non-memory deficits to occur (Reid *et al.*, 1996; Perry *et al.*, 2000). Many studies have found marked deficits in: (i) the

ability to divide attention (Baddeley *et al.*, 1986, 1991, 2001; Grober and Sliwinski, 1991; Morris, 1994; Della Sala *et al.*, 1995); (ii) selective attention (Stuart-Hamilton *et al.*, 1988; Cossa *et al.*, 1989; Mohr *et al.*, 1990; Della Sala *et al.*, 1992; Foldi *et al.*, 1992; Parasuraman *et al.*, 1995; Simone and Baylis, 1997); and (iii) tasks involving executive control functions (Binetti *et al.*, 1993; Laflèche and Albert, 1995; Patterson *et al.*, 1996; Collette *et al.*, 1999a). On the other hand, the ability to maintain vigilance is relatively preserved in the early stages of Alzheimer's disease, particularly if a task involves little cognitive effort (Nebes and Brady, 1993). However, Baddeley *et al.* (1999) showed that this ability is reduced

when the task involves more effortful processes, such as maintaining the representation of a visual stimulus over a period of time.

The study of Perry *et al.* (2000) revealed that not all subtypes of attention were equally impaired in Alzheimer's disease. The attentional tasks particularly affected were those involving response inhibition, target selection or switching. These findings were consistent with Perry and Hodges' (1999) comprehensive review of attentional and executive deficits in Alzheimer's disease, in which it was suggested that facilitatory functions of attention, such as detecting targets, were relatively preserved, whereas coping with the interference was particularly impaired. Thus, the failure of inhibitory processing in Alzheimer's disease patients may characterize their attentional deficits.

However, one must be wary of interpreting such inhibitory deficits as a process-specific change in Alzheimer's disease. Other cognitive impairments occur in the early stages of Alzheimer's disease, such as a pronounced slowing in processing speed. Indeed, Alzheimer's disease is responsible for an increase in response latencies on nearly all cognitive tasks (Nebes and Madden, 1988; Gordon and Carson, 1990; Nebes and Brady, 1992). This increase is more marked in complex and attentionally demanding tasks (Nestor *et al.*, 1991) and is assumed to result from a combination of both motor and cognitive slowing (Nebes *et al.*, 1998). Thus, declines in processing speed may mediate dementia-related cognitive changes in a similar fashion to the potential role of slowing in the normal ageing process. Salthouse (1996) outlines a processing speed theory of age-associated cognitive change. According to this view, much of what is classed as a process-specific impairment of memory or attention with age could be accounted for by a more general deficit in processing speed. However, the role of slowing in age-related and dementia-related cognitive changes may not be the same. Sliwinski and Buschke (1997), for example, examined the role of slowing in the performance of elderly adults and patients with Alzheimer's disease in different memory tasks, such as cued memory tasks and logical memory tests. Statistical control of processing speed substantially attenuated age-related variance in memory but did not attenuate much of the dementia-related variance, suggesting that a reduction in processing speed cannot by itself account for the cognitive deterioration occurring in Alzheimer's disease.

The purpose of the present review is to outline the pattern of inhibitory deficits associated with Alzheimer's disease and to discuss the nature of these deficits. In particular, we aim to address whether all inhibitory processes decline in Alzheimer's disease, whether the available evidence allows understanding of the cognitive causes of these deficits, and whether more general information processing changes in Alzheimer's disease, such as slowed processing, underlie poor performance on the inhibition tasks.

### ***Inhibition deficits: a working definition***

Since the time of Luria (1961), who argued that inhibitory processes play a crucial role in human cognition, the concept of inhibition has had a long career in cognitive psychology. The operational definition of inhibition differs depending on whether the conceptual framework in which inhibitory processes are described is selective attention (Neill, 1977; Dempster, 1992; Houghton and Tipper, 1994), visual attention (Posner and Snyder, 1975), working memory (Zacks and Hasher, 1994) or language (Gernsbacher and Faust, 1991). Despite the diversity of models, Bjorklund and Harnishfeger (1995) proposed a comprehensive definition of inhibitory processes. They define inhibition as the ensemble of processes which allow the suppression of previously activated cognitive contents, the clearing of irrelevant actions or attentional focus from consciousness, and the resistance to interference from potentially attention-capturing stimuli. Inhibitory failures are considered to be central to many psychological disorders, such as hyperactivity, anxiety, depression, schizophrenia, post-traumatic stress and obsessive-compulsive disorder (for a review see Nigg, 2000).

There is widespread agreement that there are multiple inhibitory systems rather than a monolithic process that covers all aspects of inhibiting thoughts, responses and behaviours (Dempster, 1991; Connelly and Hasher, 1993; Kramer *et al.*, 1994; Bjorklund and Harnishfeger, 1995; Nigg, 2000). Such fractionation was introduced to account for the divergent results reported in studies of normal ageing when inhibitory functions were measured by different tasks (Connelly and Hasher, 1993; Kramer *et al.*, 1994). Additionally, inhibitory mechanisms have been described as playing a role in orchestrating cognitive performance in various domains of cognition (Clark, 1996; Kok, 1999) or supervisory attentional processes (Norman and Shallice, 1986). This particular status of inhibitory processes makes them interesting to study in Alzheimer's disease. Indeed, because they are known to interact with numerous domains of cognition, it would be conceivable to postulate that a dysfunction of these processes could partially account for cognitive deficits traditionally attributed to other impairments, such as memory dysfunctions.

Hasher and Zacks (1988) originally suggested that impaired inhibitory processes may explain some of the cognitive changes associated with normal ageing, as inefficient inhibitory mechanisms could hamper selective attention, causing the ingression of task-irrelevant information into working memory. This specific cognitive impairment could explain both the increased processing time and the decreased recognition and recall abilities observed in normal ageing (e.g. West, 1999). Although the inhibition theory of cognitive ageing has been widely criticized (e.g. McDowd, 1997), recently it has generated a large number of experimental ageing studies (Burke, 1997).

It is clear that the concept of 'inhibition' covers many different levels of cognitive processing. Inhibitory processes

may act upon thoughts, verbal responses, visual processing, sounds, actions, or semantic processing. One brain area may be thought of as inhibiting the activation of another, and the activity of neurons may be inhibited by certain neurotransmitters. The extent to which inhibitory processes can be considered analogous across these different domains is not clear (Rabbitt, 1997). Rabbitt *et al.* (2001) highlighted the problem of using the overarching term 'inhibition' when there is no clear definition of what does and does not fall under this umbrella. Although there are many different behavioural tasks of inhibition that are widely used in the cognitive and neuropsychological literature (classic examples being the Stroop task, negative priming, the go-no go task, antisaccades, inhibition of return, directed forgetting and retrieval-induced forgetting; all these are outlined below), it is not clear whether each of these tasks taps a different inhibitory process or whether each task can be classified into different categories of inhibition.

Correlations between different inhibitory measures are generally rather low (e.g. Kramer *et al.*, 1994). Even when inhibitory processing demands in two tasks appear similar (e.g. inhibiting the automatic reading of words versus the automatic reading of numbers) there are poor correlations in normal populations (Ward *et al.*, 2001; Shilling *et al.*, 2002). Relatively little is understood about the nature of inhibitory processing in the different paradigms frequently used to assess inhibition, and poor performance may also reflect other types of cognitive deficits, such as slowed processing, low levels of activation of the most relevant material, and problems in coordinating multiple task demands. Indeed, some authors have argued that we do not need the construct of inhibition at all to explain performance on tasks such as Stroop and negative priming (e.g. Kimberg and Farah, 1993; Neill *et al.*, 1995).

In general, in the literature on Alzheimer's disease there has been little consideration as to whether poor performance on inhibition paradigms reflects a deficit of inhibitory processing or other types of cognitive deficit. This seems an important question to address in view of the many changes in cognition that characterize Alzheimer's disease. Further, few studies have assessed whether poor performance on inhibition tasks in Alzheimer's disease are intercorrelated or reflect separable deficits. Also, so far there has been no overview of the literature on Alzheimer's disease and inhibition tasks that gives a broad picture of whether Alzheimer's disease affects performance across all aspects of inhibitory processing.

### ***Aims of the present review***

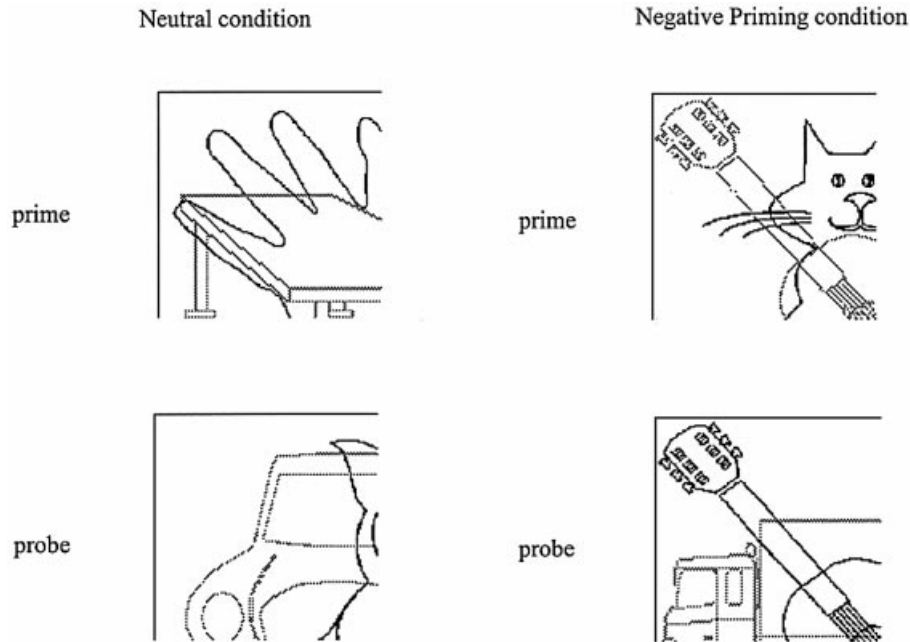
The purpose of the present article is to critically review studies that assess inhibitory functioning in Alzheimer's disease. Studies were selected by means of a literature search in PsycLit and MedLine using the keywords 'attention', 'inhibition' and 'suppression', and terms labelling the different inhibitory paradigms (e.g. 'negative priming', 'Stroop', etc.), all crossed with 'Alzheimer' or 'dementia'.

Additional studies were identified by hand-searching references cited in these studies. The first issue is to determine whether deficits on inhibitory paradigms are more frequent or more severe in Alzheimer's disease than in normal ageing. The second issue is to establish whether all types of inhibitory mechanisms are equally affected in Alzheimer's disease or whether the disease affects some mechanisms selectively while sparing others, and if so, what could be the possible explanation for this selective damage. To address these questions, we will review experiments that use paradigms allowing direct assessment of measures of inhibitory functioning as well as experiments from which we can imply information on the integrity of these mechanisms in Alzheimer's disease. Throughout the review we will also propose future work that needs to be carried out in order to better understand the nature of any inhibitory changes in Alzheimer's disease.

### ***Inhibition deficits in Alzheimer's disease Inhibition in working memory and episodic memory***

Deficits in aspects of Baddeley's (1986) model of working memory have been shown in Alzheimer's disease using a variety of different types of materials and procedures. This model comprises a central executive component responsible for cognitive control processes, strategy selection and the coordination of the various processes required for the temporary storage and processing of information. It also outlines domain-specific slave systems that retain and rehearse verbal and visuospatial information. Deficits related to the central executive component have been reported in Alzheimer's disease patients (see reviews in Baddeley and Della Sala, 1996; Collette *et al.*, 1999b; Della Sala and Logie, 2001). For example, experiments using the dual-task paradigm demonstrate that once each component task has been titrated for the individual participant's abilities, patients with Alzheimer's disease perform as well as elderly controls in each of the two tasks performed singly, but show disproportionate difficulty when the two tasks are performed simultaneously, independently from the cognitive demands of the component tasks (Baddeley *et al.*, 1986, 1991; Grober and Sliwinski, 1991; Morris, 1994). More recently, however, Baddeley *et al.* (2001) showed that, in addition to this dual-task processing deficit, the capacity to resist distraction could be another component involved in the executive dysfunction in Alzheimer's disease.

The bulk of the conceptual framework on the role of inhibitory processes in working memory comes from Hasher and Zack's (1988) model, in which it is suggested that inhibitory processes may serve to limit the contents of working memory to goal-oriented information. More precisely, inhibitory processes help to regulate working memory by suppressing interference from irrelevant information. When a response has been produced previously, inhibitory



**Fig. 1** The negative priming paradigm. The target picture is drawn with continuous lines and the distractor picture with dotted lines.

processes are also required to suppress the immediate recurrence of the same response, where it is no longer the correct response to a new stimulus.

Perseverations in verbal memory tasks may therefore reflect the difficulty in suppressing previously named target words, and intrusions may be due to difficulty in suppressing extra-list words, which are either words activated by semantic or phonemic associations with words that are to be named, or delayed responses to previously presented test material. Increased rates of irrelevant intrusions in speech (Gold *et al.*, 1988) and in verbal memory tasks (Stine and Wingfield, 1987), as well as increased rates of repetitions (Koriat *et al.*, 1988), have been reported in normal elderly people, suggesting declining efficiency of inhibitory processes regulating working memory with age. Studies on qualitative analyses of verbal productions show that, compared with normal elderly controls, Alzheimer's disease patients commit significantly more intrusions (Bandera *et al.*, 1991; Cahn *et al.*, 1997; Le Moal *et al.*, 1997; Amieva *et al.*, 1998a) and perseverations (Sebastian *et al.*, 2001). Moreover, Fox *et al.* (1998) found that the proportion of intrusions was associated with dementia severity, the most severe Alzheimer's disease patients giving almost exclusively intrusion responses. Fuld *et al.* (1982) also showed that intrusions characterize the responses of Alzheimer's disease patients, and provided evidence of an association between intrusions, low choline acetyltransferase levels and the number of senile plaques. Nonetheless, although it seems clear that intrusions are the product of abnormal functioning in patients with dementia, the question of the specificity of intrusions to Alzheimer's disease has been debated. Intrusions have been observed also in patients affected by other forms of dementia, such as depressive

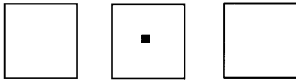
pseudodementia, Parkinson's disease and progressive supranuclear palsy (Gainotti *et al.*, 1998). However, Alzheimer's disease patients exhibit higher intrusion rates compared with those suffering from Parkinson's disease (Barrett *et al.*, 2000), vascular dementia (Lafosse *et al.*, 1997) or major depression (Loewenstein *et al.*, 1991). On the other hand, Rouleau *et al.* (2001) reported qualitative similarities in the types of intrusions made by patients suffering from Alzheimer's disease and frontal lobe dementia.

However, Alzheimer's disease does not appear to impair all inhibitory processes in memory. Moulin *et al.* (2002) found no effect of Alzheimer's disease on retrieval-induced forgetting (RIF), a task in which category-exemplar pairs are presented (e.g. fruit-melon, fruit-pear, tree-oak, tree-birch), a subset of which are then practised (e.g. fruit-melon). Participants are then asked to recall all of the category exemplars on the original list. RIF effects are indicated by poorer recall of unrehearsed members of a category from which other members have been rehearsed (from the example above: fruit-pear) compared with recall of members from completely unrehearsed categories (e.g. tree-oak or tree-birch). Both older controls and Alzheimer's disease patients showed similar, strong RIF effects, suggesting that there was no Alzheimer's disease-related deficit in the automatic inhibition of non-rehearsed items from within a semantic category.

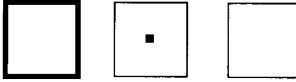
### ***Inhibition in selective attention***

Neill (1977) posits that facilitatory mechanisms operate in parallel with inhibitory mechanisms in the selection of information. This idea that inhibition is one of the funda-

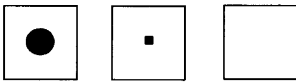
## 1. Preparation phase



## 2. Cue onset



## 3. Target appearing in the same field as the cue after a 1-2 s delay



**Fig. 2** The inhibition of return paradigm.

mental components of selective attention has been reinforced by a series of studies using the negative priming (NP) paradigm (e.g. Tipper, 1985; Neill *et al.*, 1995). NP is believed to measure the efficiency with which an individual inhibits distracting information in order to focus attention on the relevant items. In a typical NP experiment (e.g. Tipper, 1985), the stimuli are two overlapping pictures (or words or letters); one is printed in red, which the participant has to name, and one is printed in green, which the participant is instructed to ignore. In order to assess NP, participants are shown a prime trial of a target picture printed in red, with a distracting picture printed in green, followed by a probe trial, in which the red target picture to be named is the same as the distracting picture from the prime trial (Fig. 1). In younger adults, an increase in response latency in these critical NP trials (compared with control trials) is usually observed, which is thought to reflect inhibition of internal representation of distracting information in the prime trial (Houghton and Tipper, 1994).

Whether or not the NP effect is susceptible to normal ageing is a matter of controversy. Whereas some studies report that the magnitude of NP effects is equivalent for elderly and young adults (Sullivan and Faust, 1993; Kramer *et al.*, 1994; Schooler *et al.*, 1997; Langley *et al.*, 1998), others fail to demonstrate NP effects in older adults (Hasher *et al.*, 1991; McDowd and Oseas-Kreger, 1991; Tipper, 1991; Stoltzfus *et al.*, 1993). Whilst a lack of NP would suggest a failure in inhibitory mechanisms in older adults, the small size of the NP effect, together with the increased variability of performance in older individuals, might explain the lack of NP effect in some of these studies.

Given the reported deficits in selective attention shown by Alzheimer's disease patients (e.g. Stuart-Hamilton *et al.*, 1988; Mohr *et al.*, 1990; Foldi *et al.*, 1992; Parasuraman *et al.*, 1995; Simone and Baylis, 1997), it seems reasonable to investigate NP in this population. However, there have been relatively few studies carried out, and the results are not straightforward. Sullivan *et al.* (1995) presented a pictorial NP task to healthy younger and older participants and to

Alzheimer's disease patients. They found significant NP effects in the majority of younger and older adults, but less reliable NP effects in Alzheimer's disease patients. In a second experiment, Sullivan *et al.* (1995) looked at NP effects using words as stimuli. Here there was a clear difference between the significant NP shown in older adults and the lack of NP effects shown in Alzheimer's disease patients, and it was concluded that Alzheimer's disease is associated with a reduced ability to inhibit distracting information. Using pictorial stimuli, Amieva *et al.* (2002) also found that Alzheimer's disease patients showed no significant evidence of NP. However, whilst these results suggest that Alzheimer's disease patients are not successfully inhibiting irrelevant information in prime trials in NP, an alternative explanation is that patients fail to retrieve information associated with repeated primes in NP experiments because of an episodic memory deficit (Sullivan *et al.*, 1995). No study has directly investigated whether the effects of Alzheimer's disease on NP are likely to be due to inhibitory problems or episodic retrieval difficulties, although Amieva *et al.* found no difference between controls and Alzheimer's disease patients in baseline picture-naming latency, suggesting that the impaired NP effect is unlikely to be a consequence of generally slowed task processing.

However, one study indicates that Alzheimer's disease patients can show preserved NP effects. Langley *et al.* (1998) investigated the effects of Alzheimer's disease on letter-naming NP tasks in which each trial required the naming of a letter while ignoring another letter printed in a different colour. Young, old and Alzheimer's disease groups showed significant NP effects, with a trend for larger NP effects in the Alzheimer's disease patients. Methodological differences between the NP studies may account for their different findings. Sullivan *et al.* and Amieva *et al.* used more complex stimuli (words/pictures as opposed to letters), which were presented for short durations on a computer screen; in the Langley *et al.* study, lists of stimuli were presented on cards until the participant had made all their responses. It is possible that the paradigm used by Langley *et al.* introduced an additional selective attention load whereby, in NP blocks of trials, the participants had to inhibit surrounding trials as well as distracting information from the current trial. This may have resulted in Alzheimer's disease patients taking a particularly long time to work through the NP block because of failure to inhibit information in surrounding trials rather than success in inhibiting immediately preceding distracting information. Further studies of the effects of Alzheimer's disease on NP are required in order to delineate more clearly the situations under which Alzheimer's disease patients do or do not show NP, as well as the cognitive mechanisms that might underlie any Alzheimer's disease deficit in NP.

Some inhibitory mechanisms operating in spatial selective attention appear to be preserved in Alzheimer's disease, namely the mechanisms underlying inhibition of return (IOR) (Posner and Cohen, 1984). In IOR paradigms (Fig. 2), a cue is presented in an area of the visual field, followed by a delay of

**Table 1** Study-level statistics for patients with Alzheimer's disease relative to healthy controls on the Stroop baseline and interference conditions

Study	n Controls	Dementia severity Patients	Stroop format	Baseline (B) latency (ms)	Interference (I) latency (ms) Control	Effect size ( <i>r</i> ) Alzheimer's disease	Control	Alzheimer's disease	B	I
Amieva <i>et al.</i> (2002)	28	28	Mild	Individual	644.0	626.0	974.0	1191.0	-0.05	0.33
Bondi <i>et al.</i> (2002)	51	22	Very mild	Block	838.0	1018.1	1562.5	2486.2	0.30	0.46
Bondi <i>et al.</i> (2002)	51*	25	Mild	Block	838.0	1308.1	1562.5	3719.0	0.55	0.64
Bondi <i>et al.</i> (2002)	51*	12	Moderate	Block	838.0	1367.8	1562.5	5232.6	0.49	0.63
Spieler <i>et al.</i> (1996)	25	22	Very mild	Individual	813.0	915.0	1069.0	1404.0	0.33	0.51
Spieler <i>et al.</i> (1996)	25*	40	Mild	Individual	813.0	1299.0	1069.0	1853.0	0.49	0.66
Koss <i>et al.</i> (1984)	11	9	Mild	Block	855.0	2035.0	1640.0	9305.0	0.65	0.81
Koss <i>et al.</i> (1984)	11*	5	Moderate	Block	855.0	5460.0	1640.0	11390.0	0.97	0.95
Fisher <i>et al.</i> (1990)	36	36	Moderate	Block	693.4	1376.1	1347.3	4639.2	0.76	0.77
Collette <i>et al.</i> (2002)	26	19	Not stated	Block	710.0	954.7	1303.0	2699.0	0.43	0.48
Zappoli <i>et al.</i> (1995) <sup>†</sup>	10	12	Presenile	Block	—	—	—	—	0.57	0.90

\*Participants already included in table; it should be noted that each participant contributed only once to the calculation of mean effect sizes.

<sup>†</sup>Stroop performance could not be converted to latency per stimulus and so was not included in the Brinley plot analysis. However, effect sizes could be calculated from data available in the paper, so this study was included in the meta-analysis.

1–2 s during which a central fixation cue may also appear. Subsequent presentations of targets in the area of the initial cue are responded to more slowly than targets in another area of the visual field. The IOR effect is thought to reflect a bias of attention towards novel events.

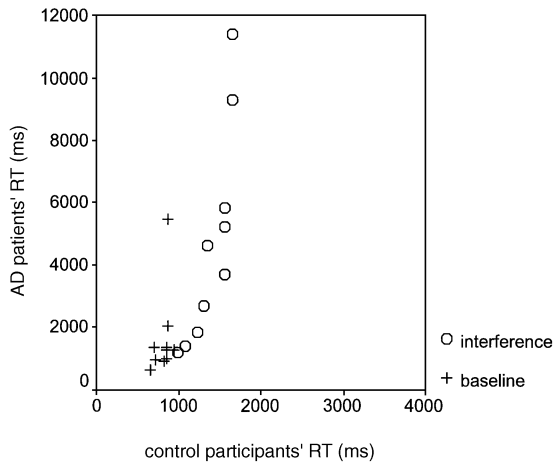
There is evidence that the delay results in an attentional shift away from the cue to another area of the visual field. The slowing of target detection in these trials (compared with trials in which no cue is presented) suggests that IOR is a phenomenon of spatial attention temporarily inhibiting an area of the environment, and redirecting attention towards other areas in which novel events may occur. IOR is preserved in normal ageing (Hartley and Kieley, 1995) and the convergent outcomes of two independent studies show that this is also the case in Alzheimer's disease (Danckert *et al.*, 1998; Faust and Balota, 1997). Recently, Langley *et al.* (2001) tested the IOR phenomenon in normal elderly adults and Alzheimer's disease patients in tasks requiring categorization as well as detection responses. In a detection IOR task they confirmed the above findings, i.e. intact IOR effects in Alzheimer's disease. However, in the categorization task the presence of IOR effects in Alzheimer's disease was less reliable, indicating some possible impairment of inhibitory processes where the material must be processed semantically rather than in terms of location.

### ***Inhibition of compelling verbal responses***

Effects of Alzheimer's disease have also been shown on what has been called the gold standard of attentional measures (MacLeod, 1992): the Stroop test (Stroop, 1935). The classic effect (known as the Stroop interference effect) is that the latency to name the colour of the ink in which a word is printed is longer when this word is the name of a colour

incongruent with the ink colour (i.e. the word blue printed in green ink), relative to the baseline condition where there is no incongruence (i.e. the word blue printed in blue ink). The Stroop effect provides evidence of difficulty in inhibiting an overlearned response, such as the automatic reading process. Stroop interference effects have been argued to increase with age (Comalli *et al.*, 1962; Cohn *et al.*, 1984; Houx *et al.*, 1993; Dulaney and Rogers, 1994; Klein *et al.*, 1997). However, several studies have shed doubt on the conclusion that normal ageing effects on Stroop performance reflect poorer inhibition of colour word reading (e.g. Boone *et al.*, 1990; Uttl and Graf, 1997; Shilling *et al.*, 2002), arguing instead that the effects of age on Stroop tasks may reflect general cognitive slowing. Verhaeghen and De Meersman (1998) conducted a meta-analysis of age-Stroop studies, in which both effect size and regression analyses indicated no differential ageing effect on interference colour naming compared with baseline naming. These findings indicate that age-related changes in Stroop performance may reflect a general slowing of processing speed as opposed to a specific deficit of inhibition (for an alternative viewpoint see West and Alain, 2000).

Typically, Stroop effects are considerably larger in Alzheimer's disease patients compared with healthy elderly controls (Koss *et al.*, 1984; Fisher *et al.*, 1990) and this has been construed as evidence that Alzheimer's disease patients experience greater difficulty in inhibiting the automatic process of reading. Koss *et al.* (1984) demonstrated that even when interference scores are adjusted for processing speed, Alzheimer's disease patients still show large Stroop effects. This interpretation is supported by the study of Spieler *et al.* (1996), in which it was found that, relative to healthy controls, Alzheimer's disease patients not only made a higher proportion of intrusive errors when naming the



**Fig. 3** Brinley plot of the mean latency of performance of Alzheimer's disease patients on the Stroop task plotted against latencies of control participants. Crosses indicate performance in the baseline condition and open circles indicate performance in the interference condition.

incongruent stimuli of the Stroop test, but also presented with greater facilitation in naming congruent colour–word stimuli. These results were interpreted as evidence for a response inhibition deficit because Alzheimer's disease patients failed to develop a controlled processing strategy.

Bondi *et al.* (2002) confirmed the effects of Alzheimer's disease on Stroop interference scores, corrected for baseline colour-naming speed, and also found that Alzheimer's disease patients made more intrusion errors. Principal component analysis revealed that speed on the interference condition loaded more highly on a visual processing factor than on semantic–verbal or executive function factors. The authors argue that Alzheimer's disease patients are less able to activate semantic representations when attempting to name the colour of ink, and this forces greater reliance on visual processing in the interference condition. They also reported that Stroop interference scores (corrected for baseline) relate to the number of neurofibrillary tangles found post-mortem in hippocampal and temporal lobe regions of the brain, but not to tangles in frontal and parietal regions. This indicates that there is unlikely to be a straightforward relationship between measures of inhibition in Alzheimer's disease and localized frontal lobe pathology.

The traditional Stroop paradigm is the only inhibition task for which sufficient studies have been reported in Alzheimer's disease to allow secondary analysis. We therefore conducted a meta-analysis to investigate whether the magnitude of the effect of Alzheimer's disease on the Stroop interference condition differed from the corresponding effect on the baseline condition. Studies were selected if they contained precise descriptive statistics for both colour–ink naming of neutral stimuli (baseline condition) and colour–ink naming of colour words (interference condition) for Alzheimer's disease patients and matched elderly controls.

The basis of meta-analytic methodology is the effect size, a standardized statistic that quantifies the magnitude of an effect. In the present study the effect size  $r$  was employed, which corresponds to the degree of correlation between group membership (i.e. Alzheimer's disease versus healthy elderly) and performance on the Stroop condition of interest. For each of the two conditions, study-level effects were pooled using the random effects model to derive an estimate of the mean, with each effect weighted for sample size to correct for sampling error.

It can be seen in Table 1 that seven studies with a total of 417 participants were included in these analyses (230 Alzheimer's disease patients and 187 controls). The meta-analysis revealed that, whilst both mean effects were significantly different from zero ( $P < 0.001$ ) and could be considered large in magnitude, the effect for the interference condition was substantially in excess of that for the baseline condition ( $r_s = 0.67$  and  $0.46$  respectively). Squares of the effect size multiplied by 100 were also calculated as these latter quantities represent the percentage of the variance ( $PV$ ) on each condition that is accounted for by group membership. The difference between effect sizes is non-linear as  $r$  increases, and thus  $PV$  is the more appropriate index when comparing variables. In terms of the  $PV$  accounted for, the presence of Alzheimer's disease accounts for over twice as much variance in the interference relative to the baseline condition ( $PVs = 44.89$  versus  $21.16\%$ ). The difference between the two conditions in terms of the  $PV$  accounted for by group membership was significant when paired  $t$ -tests were applied (using number of studies to calculate  $df$ :  $t = 2.967$ ,  $df = 6$ ,  $P = 0.025$ ).

These results therefore indicate that there are larger effects of Alzheimer's disease on the inhibition relative to the baseline condition of the Stroop, contrasting with the findings of Verhaeghen and De Meersman (1998) on normal ageing, in which there was no evidence of differential age effects on interference. However, in the present study the mean effects for both the baseline and interference conditions were associated with significant heterogeneity, as indexed by the statistic  $Q$  (both  $Ps < 0.001$ ). This indicates that there are substantive differences between studies beyond sampling error. Whilst insufficient studies were included to permit a quantitative investigation of potential moderators of these effects, differences in dementia severity will account for at least some of the heterogeneity observed. Visual inspection of Table 1 suggests that, in the more advanced stages of the disease, the two Stroop conditions become harder to differentiate in terms of their relative sensitivity to Alzheimer's disease. This presumably reflects the global cognitive decline that accompanies the progression of Alzheimer's disease. Thus, future research should investigate whether restricting comparisons to mild Alzheimer's disease yields an even larger difference between the interference and baseline conditions.

We also analysed these data using regression techniques, following the method used for normal ageing described by

Verhaeghen and De Meersman (1998). Verhaeghen and De Meersman argue that the overlapping functions to describe baseline and interference conditions in normal ageing indicate that a single underlying factor (processing speed) explains age-related variance in both conditions, and therefore that there is no specific age deficit in inhibition. A non-linear model of the relationship between different group latencies generally fits the data better than a linear model, so the following equation was used to fit the Alzheimer's disease data:  $RT_{ADpatients} = b RT_{controls}^m$ . In this equation,  $RT_{ADpatients}$  describes the mean latency of performance on a Stroop condition of Alzheimer's disease patients in a particular study, and  $RT_{controls}$  is the corresponding mean latency of the elderly control participants. The parameter  $b$  describes the slope of the function, and the parameter  $m$  describes the ratio of decay rates of information loss in Alzheimer's disease patients compared with controls (Myerson *et al.*, 1990), allowing the function to be non-linear if  $m \neq 1$ . The critical question is whether the regression equations for baseline and interference conditions in the Stroop calculated separately are overlapping. If so, this indicates that only a single equation is needed to explain the effects of Alzheimer's disease in the baseline and interference conditions. The mean latencies for Alzheimer's disease versus control participants are plotted in Fig. 3. When only baseline performance is considered, the slope parameter  $b = 0.02$  with the 95% confidence interval from  $-0.85$  to  $0.88$ , and the power parameter  $m = 1.69$ , with the 95% confidence interval from  $-4.70$  to  $8.08$ ; however, in this case  $R^2$  was only  $0.10$ , so very little of the Alzheimer's disease variance in reaction time was explained by control participants variance. For the interference condition,  $b = 3.8 \times 10^{-4}$ , with the 95% confidence interval from  $-7.16 \times 10^{-3}$  to  $7.94 \times 10^{-3}$ , and  $m = 2.26$ , with the confidence interval from  $-0.40$  to  $4.92$ ; in this case  $R^2 = 0.61$ . In the baseline condition, the estimated value of the slope,  $b$ , does fall outside of the confidence interval for the interference condition, suggesting that the two conditions may be best explained by separate functions. This would imply that Alzheimer's disease has a differential effect on interference as opposed to baseline latencies, supporting the idea of a specific inhibitory deficit separate from general slowing. However, given the small number of studies available, the low percentage of variance explained by the regression equations and the massive confidence intervals around the power parameter, these conclusions should be treated as tentative.

The Hayling task (Burgess and Shallice, 1996) assesses the capacity to suppress a verbal response that is embedded in a test of semantic processing. Participants are presented with a series of short sentences in which the last word is omitted but is easily anticipated, e.g. 'The captain wanted to stay with the sinking ...'. Participants are asked to listen to each sentence and complete it not with the predicted word but with a word unrelated to the sentence. Thus, this task requires the voluntary inhibition of a mandatory response that comes to mind. Scoring instructions specify that completing the sentence either with the expected word or with a related

word is an error. Healthy elderly are poorer than younger adults at inhibiting the expected response on this task (Andres and Van der Linden, 2000). Collette *et al.* (1999a) found no difference between controls and Alzheimer's disease patients in terms of speed of responding on the interference trials. However, the overall semantic relatedness of the response to the sentence was considerably higher in the Alzheimer's disease patients, which suggests that the patients had weaker ability to inhibit semantically related but task-irrelevant responses. They also report that there was no relationship between a measure of processing speed and semantic relatedness of words produced in the Hayling task, whereas processing speed did predict performance on a number of other executive function measures. These results can be interpreted as a specific deficit of controlled semantic inhibition in Alzheimer's disease, independent of changes in processing speed.

### ***Inhibition of compelling motor responses***

The ability to suppress saccadic eye movements intentionally has been used to assess motor response inhibition of reflexive responses (Müller and Rabbitt, 1989). The antisaccade task requires participants to inhibit a reflexive saccade directed towards a peripheral onset cue (prosaccade) and instead generate a saccade in the opposite direction (antisaccade). The ability to control saccadic eye movements decreases with age (Olincy *et al.*, 1997; Nieuwenhuis *et al.*, 2000) and seems to be even more affected by the presence of Alzheimer's disease. Alzheimer's disease patients have been shown to make more errors on antisaccade trials than elderly controls (Mulligan *et al.*, 1996) and the frequency of prosaccade errors made on antisaccade trials correlates with the severity of dementia (Currie *et al.*, 1991).

Marked deficits were also found by Simone and Baylis (1997) using a selective reaching task. The participants were presented with nine possible key locations appearing on a screen in front of them, among which the target location appeared in red and the distracter in green. They were asked to move their hand from a home key to press the red target as quickly as possible and to ignore the distracter key. The authors described Alzheimer's disease patients' performance as reflecting a catastrophic failure of inhibitory mechanisms, since the patients exhibited severe difficulty in preventing responses to distracters, even though they were aware that these responses were incorrect. The authors also demonstrated that the probability of making responses to distracters was related to disease severity.

The go-no go and stop signal tests are the two main paradigms used to explore motor response inhibition. In the former, participants engage in a successive choice reaction time task involving trials in which they have to respond to a given target stimulus and trials in which they have to withhold their response to another stimulus. Thus, the go-no go paradigm is assumed to involve the execution ('go' trials) and the inhibition ('no go' trials) of a prepared motor



**Table 2** Effects of Alzheimer's disease on the main paradigms used to assess inhibition.

Experimental paradigm	Study	Alzheimer's disease performance compared with controls	Modality of inhibition: what type of process must be inhibited?	Automatic or controlled inhibition required?
Inhibition of return (detection paradigm)	Danckert <i>et al.</i> (1998)	Normal	Spatial orienting	Automatic
Retrieval-induced forgetting	Faust and Balota (1997) Langley <i>et al.</i> (2001) Moulin <i>et al.</i> (2002)	Normal Normal Normal	Semantic activation	Automatic
Negative priming	Amieva <i>et al.</i> (2002) Sullivan <i>et al.</i> (1995) Langley <i>et al.</i> (1998)	Severely abnormal Severely abnormal Normal	Visual processing	Controlled
Go–no go	Amieva <i>et al.</i> (2002) Collette <i>et al.</i> (2002)	NormalAbnormal	Motor response	Controlled
Stop signal	Amieva <i>et al.</i> (2002)	Abnormal	Motor response	Controlled
Hayling task	Collette <i>et al.</i> (1999a)	Severely abnormal	Verbal semantic response	Controlled
Trail-making task	Collette <i>et al.</i> (2002) Amieva <i>et al.</i> (1998b)	Abnormal Severely abnormal	Semantic activation and motor response	Controlled
Stroop task	See list of papers in Table 1	Severely abnormal	Verbal semantic response	Controlled
Antisaccade task	Currie <i>et al.</i> (1991) Mulligan <i>et al.</i> (1996)	Severely abnormal Severely abnormal	Orienting response to visual information	Controlled

response. In the stop signal paradigm (Logan and Cowan, 1984) participants are asked to perform a visual choice reaction time task and to abort their response on the relatively infrequent occasions on which they hear a signal tone. This paradigm therefore provides a way to assess the ability to voluntarily inhibit a response driven by an external cue.

In the go–no go task, Amieva *et al.* (2002) found little evidence for impaired inhibition of prepared motor responses in Alzheimer's disease. Response latencies on the 'go' trials were significantly longer for the Alzheimer's disease patients than for the elderly controls. However, Alzheimer's disease patients were also slower at a simple reaction time task, and when the ratio of time on 'go' trials to simple reaction time was calculated there was no effect of Alzheimer's disease. Also, there were no group differences in the number of errors made on the go–no go task. This suggests that any effects of Alzheimer's disease on this version of the go–no go task can be attributed to slowed information processing rather than inhibitory failures. In contrast, Collette *et al.* (2002) found no difference in latency of 'go' trials between Alzheimer's disease and control groups, but a significant decrease in the number of correct responses made by the Alzheimer's disease group. However, in both of these studies, 50% of trials were 'go' trials and 50% 'no go' trials. This would have resulted in relatively weak reinforcement of the motor response to 'go' trials, and therefore the extent to which this version of the task actually demands response inhibition is unclear. Increasing the frequency of 'go' trials is known to result in stronger response preparation in young adults (Low and Miller, 1999), making the response suppression harder (Bruin and Wijers,

2002). Thus we predict that increasing the 'go' response probability in the go–no go paradigm would cause more overt deficits in Alzheimer's disease patients.

Amieva *et al.* (2002) examined the effects of Alzheimer's disease on a stop signal task in which a tone appeared after presentation of some of the stimuli, indicating that a response should not be made to that trial. When a ratio of response times on 'go' trials on the stop signal task to choice reaction time was calculated, Alzheimer's disease patients exhibited slowing equivalent to that of elderly controls. The main inhibitory measure taken from the stop signal task is the number of errors (making a motor response despite the signal tone on the 'stop' trials), and Alzheimer's disease patients were more likely to make such errors than elderly controls, suggesting impairment in the Alzheimer's disease group in dealing with inhibition of a prepotent motor plan.

### ***Inhibition and shifting abilities***

Inhibitory deficits may also contribute to the decline in mental flexibility in Alzheimer's disease, as suggested by the few studies investigating qualitative features of the performance of Alzheimer's disease patients in traditional tests requiring cognitive shifting. For instance, Paolo *et al.* (1996) reported that Alzheimer's disease patients were less able than elderly controls to discover new rules in the Wisconsin Card Sorting Test (Heaton, 1981). Bondi *et al.* (1993) also reported more frequent perseverative errors by the Alzheimer's disease patients on this test, and argued that this reflected difficulty in suppressing the previously activated rule.

A detailed error analysis was carried out on the performance of Alzheimer's disease patients on the Trail Making task (Amieva *et al.*, 1998b). The critical inhibition trial on this task requires participants to alternately connect circles containing numbers and letters, following their respective sequences (1A2B3C, etc.). The patterns of errors made by Alzheimer's disease patients and elderly controls differed qualitatively. Most errors committed by the patients (67%) were either due to the tendency to connect with the spatially nearest item or to the difficulty in suppressing the automatic overlearned sequence of numbers (or letters). The core feature of these errors was the failure to suppress irrelevant information or operations. Elderly controls rarely committed these 'inhibition errors', which appeared to be specific to the Alzheimer's disease patients.

## Discussion

Table 2 summarizes the effects of Alzheimer's disease on the basic paradigms most frequently used to assess aspects of inhibition, and offers a classification of each inhibition task in terms of the process that has to be inhibited and the automaticity of the inhibitory process involved.

From the majority of studies reviewed, it can be concluded that Alzheimer's disease is typified by a noteworthy impairment of inhibitory mechanisms, and that there is more than one reason to include measures of inhibitory functioning in clinical assessment of the disorder. The facts that these deficits are considerably larger in Alzheimer's disease than in normal ageing and that on some paradigms there are qualitative differences in the type of inhibitory errors made makes them an interesting potential diagnostic aid. For the same reasons, inhibitory measures would make an interesting tool to follow up the progression of the disease in longitudinal studies or in pharmaceutical trials. Drugs that modify the cholinergic system, such as acetylcholinesterase inhibitors, have been shown to improve the performance of Alzheimer's disease patients in attentional rather than memory tasks (Sahakian and Coull, 1993; Lawrence and Sahakian, 1995). Hence, it would be of particular interest to investigate whether the attentional improvement induced by cholinergic drugs is paralleled by an improvement of inhibitory functioning. Unfortunately, therapeutic trials that assess the efficacy of such drug therapies in Alzheimer's disease typically do not include inhibitory measures, leaving room for future research to address this issue.

Concerning the question of whether Alzheimer's disease affects all inhibitory mechanisms equally or only a subset of them, this review indicates that most of the inhibitory mechanisms tested so far are affected by Alzheimer's disease. However, a few measures of inhibition, such as IOR, are relatively spared. Thus, even though some types of inhibitory failures in Alzheimer's disease are reliable and of large magnitude, they are unlikely to reflect a breakdown of all inhibitory mechanisms. However, different groups of patients have been tested on each inhibition paradigm, and there are a

number of potentially important moderators of effects, including the level of Alzheimer's disease severity, the age of the patients, and educational level. Stronger support for the hypothesis of selective inhibitory failures in Alzheimer's disease would be provided if a variety of tasks presumed to tap different inhibitory mechanisms were examined within the same patient group. Amieva *et al.* (2002) investigated the effects of mild Alzheimer's disease on four inhibitory paradigms within the same patient group: the NP paradigm, the Stroop test, the go-no go task and the stop signal task. The results showed impaired inhibition on the NP, Stroop and stop signal tasks, but no impairment on the go-no go task.

More generally, the accrued research on the effects of Alzheimer's disease on inhibition suggests that a range of different mechanisms sustain inhibitory processes, which raises questions about the use of the term 'inhibition' as though it describes a single cognitive phenomenon. This conclusion, deriving from the present review of studies of Alzheimer's disease, is supported by other studies on normal ageing (Connelly and Hasher, 1993; Kramer *et al.*, 1994) and on individual differences (Ward *et al.*, 2001; Shilling *et al.*, 2002) which indicate that inhibition should not be conceived as a unitary, homogeneous function. There is still some room to better specify the different processes of inhibition and their relation to one another. Moulin *et al.* (2002, p. 865) argue that 'The exciting possibility exists that Alzheimer's disease could be used as a tool to help cognitive psychologists examine different forms of inhibition'.

It would be valuable to understand why Alzheimer's disease selectively affects some inhibitory mechanisms while sparing others, like those taxed by IOR and RIF tasks. Below, a number of such possibilities are considered: modality of inhibition, whether the inhibitory processing acts upon thoughts or responses, and whether the inhibition required is mostly automatic or controlled (see also Table 2, which classifies all of the major inhibition tasks in relation to these distinctions).

One possibility would be that Alzheimer's disease selectively impairs inhibitory processes acting on a particular modality, such as verbal, visual or motor processing. Whilst this seems unlikely, given that Alzheimer's disease impairments of inhibition may occur across verbal (e.g. Hayling task), motor (stop signal) and visual (NP) modalities, no study has directly investigated whether varying the modality of information to be inhibited moderates the magnitude of Alzheimer's disease effects. It would be useful in future studies to see whether Alzheimer's disease has differential effects on, for example, object and spatial NP within a single sample of patients.

Another important distinction is between inhibition of behavioural responses as opposed to inhibition of cognitive processes (Bjorklund and Harnishfeger, 1995). Most of the tasks that involve response inhibition (e.g. Stroop, anti-saccades) do show Alzheimer's disease-related impairment, while tasks in which the inhibition is of covert perceptual or semantic processes rather than overt responses are typically

relatively unimpaired (e.g. IOR, RIF). However, there are also examples of response inhibition tasks in which Alzheimer's disease effects are absent in some studies (e.g. go-no go) and perceptual inhibition tasks in which Alzheimer's disease effects are present (e.g. NP).

Another way in which inhibitory tasks may be classified reflects the extent to which they require controlled conscious inhibition versus automatic processes of inhibition operating below the level of conscious control. Nigg (2000), in an extensive review of inhibitory deficits across a wide range of psychopathological conditions, proposes that this distinction is the best way of classifying inhibition tasks. Others have suggested (e.g. Moulin *et al.*, 2002) that automatic processes of inhibition may be unaffected by Alzheimer's disease while deliberate inhibitory processes are impaired. In relation to this distinction, it is interesting to note that IOR has been defined as a reflexive phenomenon. According to Rafal and Henik (1994), IOR occurs following visual signals directly activating the oculomotor system independent of voluntary control. Thus, IOR does not result from inner driven shifts of attention but rather is activated during reflexive orienting of attention. The fact that IOR taps into a reflexive system may be important. Indeed, Langley *et al.* (2001) used a more complex IOR paradigm involving semantic judgements, and showed that whenever the IOR task requires conscious and effortful processes, Alzheimer's disease patients no longer exhibit IOR effects, while elderly adults still do.

Thus, the distinction between automatic, reflexive inhibitory mechanisms and controlled inhibitory mechanisms may provide us with an account of the pattern of performance of Alzheimer's disease patients. It is also important to consider the cognitive operations on which inhibitory mechanisms are to be exerted. Houghton and Tipper (1994) stated that 'the strength of the inhibition continually adapts to the strength of the to-be-ignored inputs' (p. 107). In other words, the strength of the cognitive operation/content that has to be suppressed will determine the degree of effortfulness of the mechanisms applied to inhibit it. Most of the tasks in which Alzheimer's disease patients experience difficulties share the characteristic that the process to be suppressed is salient or mandatory, and therefore the inhibitory processing required is relatively effortful and controlled. The Stroop test calls for the inhibition of the overlearned mandatory process of reading the names of colours, the Hayling task of the most obvious word that springs to mind, and the antisaccade task of a reflexive saccade directed towards a peripheral cue.

In relation to this classification, it is interesting to consider whether NP can be considered to involve controlled inhibitory processing. The inhibitory processes in NP paradigms are sometimes regarded as relatively automated (e.g. Langley *et al.*, 1998). However, according to Houghton and Tipper (1994), whereas IOR is the result of a 'non intentional grabbing' of attention by an external stimulus (exogenous selection), the NP effect occurs as a result of voluntary selective attention (endogenous selection). In at least some NP experiments, the instructions may lead participants to

attempt to actively suppress the distracter stimulus. For example, Sullivan *et al.* (1995, p. 542) told participants 'The green picture is there to make the task more difficult ... the more you can ignore the green picture the better you will be able to name the red picture'. In addition, in older adults the NP effect needs some practice to develop (e.g. Amieva *et al.*, 2002), and performing NP concurrently with a secondary task can eliminate the NP effect in healthy young adults (Engle *et al.*, 1995; Conway *et al.*, 1999), suggesting that NP is not necessarily a mandatory mechanism triggered by external stimuli.

It is also possible that, in NP tasks, the process to be suppressed (usually naming) demands more active processing for Alzheimer's disease patients than for young participants. The task of distinguishing between two line drawings, for example, is very easy for young adults but is considerably more difficult for patients with Alzheimer's disease (Della Sala *et al.*, 1995). Alzheimer's disease was found to have no effect on NP to letter naming (Langley *et al.*, 1998), a task which is presumably relatively automatic even for patients, while Alzheimer's disease resulted in an absence of NP effects on tasks which might call for conscious control, like word-reading and picture-naming (Sullivan *et al.*, 1995; Amieva *et al.*, 2002). It would be of interest in future studies to investigate more precisely the pattern of Alzheimer's disease deficits on a range of NP tasks, and the extent to which any deficits relate to the degree of conscious control required to perform the to-be-suppressed task.

We therefore propose that the best way of classifying whether or not Alzheimer's disease is likely to cause poorer performance on a task designed to tap inhibition is to understand the extent to which the inhibitory processes required are automatic (i.e. are not subject to conscious cognitive control) versus controlled (i.e. require conscious concentration and cognitive effort). This can be seen as a continuum, from the very automatic inhibitory processes required for IOR to the very controlled suppression required for antisaccades. Even within a family of tasks, the degree of controlled suppression is likely to vary with the extent to which the activity to be inhibited is practised and mandatory; for example, in the Stroop task it is likely that a colour-word Stroop will require higher levels of controlled inhibition than in number Stroop tasks, in which there is a lower 'training ratio' (difference in levels of practice between the incompatible tasks of number counting and number reading) (Ward *et al.*, 2001). It can be seen from Table 2 that all of the tasks classified as requiring automatic inhibition show an absence of Alzheimer's disease effects, while, with one exception, all of the tasks classified as requiring controlled inhibition are impaired in Alzheimer's disease. The exception is the go-no go task; however, as discussed above, both studies involving this task have used a version likely to impose weak inhibitory demands and there are, as yet, no studies involving a lower frequency of no go responses which would place more substantial demands on controlled inhibition.

One criticism of the automatic/controlled distinction is that it may simply reflect the outcome of a difficulty effect, the 'controlled' tasks being more 'difficult'. However, difficulty may be defined in a number of ways (e.g. the number of cognitive operations involved, the perceived cognitive effort demanded by a task, the length of time taken on a task trial). Using any of these definitions of difficulty, most tasks that require controlled inhibition will be difficult compared with automatic tasks. However, some of the tasks we classify as controlled do not appear very difficult, whatever definition of difficulty is used. For example, the NP measure involves a single straightforward cognitive operation (ignoring green items); this does not seem subjectively difficult to participants, and involves effects of short duration (around 30 ms). Although the concept of difficulty might explain some of the pattern of effects reported, we propose that the concept of automatic/controlled provides a clearer and more objective way of classifying inhibition tasks, and does a better job of predicting where Alzheimer's disease effects will occur. NP and IOR tasks involve effects of similar magnitude (around 30 ms in healthy older adults), yet the more automatic inhibitory processes involved in IOR are not subject to Alzheimer's disease effects, whereas the more controlled inhibition required by NP is affected by Alzheimer's disease. Also, Stuss *et al.* (1999) provide evidence that IOR and NP effects depend on different brain areas, with abnormal IOR effects in patients with left frontal lobe lesions and abnormal NP effects in right frontal and right posterior patients. This double dissociation provides support for the idea that NP and IOR tasks differ in the specific cognitive processes (and anatomical regions) involved rather than simply differing in difficulty.

However, in order to address this issue directly it would be useful to see empirical studies within the same sample of patients in which the difficulty of the tasks is manipulated, measures of processing speed are taken, and tasks of more automatic inhibition processes (e.g. IOR) are administered along with measures of controlled inhibition processes. Although inhibition measures often correlate poorly in normal populations (e.g. Kramer *et al.*, 1994), there is little evidence on the inter-relation of different controlled inhibition measures in Alzheimer's disease patients. Further analysis of the performance of Alzheimer's disease patients on the battery of inhibition tasks reported by Amieva *et al.* (2002) reveals that there was a significant correlation between inhibition indices from NP and Stroop tasks ( $r = 0.44$ ), but correlations with the other measures (stop signal and go-no go) were not significant. More information on this issue is needed to address an important question: does Alzheimer's disease cause a general failure of a controlled inhibition mechanism that affects performance on a range of tasks, or instead does Alzheimer's disease cause poor performance on a range of inhibitory processes, each of which may be dependent on different connecting pathways in the brain?

Although inhibition has been classically associated with the prefrontal cortex (e.g. Fuster, 1993; Burgess and Shallice, 1996), a growing number of functional neuroimaging studies

are showing activation beyond prefrontal areas during inhibitory tasks. While frontal regions and their cortical connections are likely to be important in controlled inhibition tasks such as the Hayling task, Stroop and antisaccades, it has been argued that reflexive inhibition tasks such as IOR involve mainly midbrain structures such as the superior colliculus and basal ganglia (Faust and Balota, 1997; Collette and Van der Linden, 2002). In an elegant study, Lepsien and Pollmann (2002) compared the cerebral activation during two tasks of visual attention: an IOR task and a task requiring the covert reorienting of attention immediately after an invalid contralateral cue. Both these tasks require reorienting of attention, though the IOR involves automatic and unconscious reorienting whereas the other task requires voluntary reorientation of attention. The cortical areas activated during IOR were those implicated in oculomotor programming, whereas the task requiring a covert reorienting of attention activated frontal regions generally associated with attentional processes: left frontopolar regions and bilateral medial frontal gyri. This finding suggests that, when the inhibition of an attentional field is voluntarily generated, the recruitment of frontal areas is more widespread.

An orchestrated participation of various structures distributed in the brain seems to be involved in most inhibitory tasks, particularly those involving the inhibition of compelling responses, either verbal (Pardo *et al.*, 1990; Bench *et al.*, 1993) or motor (Garavan *et al.*, 1999; Rubia *et al.*, 2001). Inhibitory tasks involving more automatic processes are likely to be subserved by more localized neural systems than controlled inhibitory processes (Morris, 1996). Interestingly, the physiopathological processes of Alzheimer's disease are known to entail a breakdown in the connections between anterior cortical and posterior cortical association areas (Leuchter *et al.*, 1992; Morris, 1994, 1996). Parasuraman and Nestor (1993) proposed that some cognitive operations function normally in Alzheimer's disease because they are subserved by circumscribed neural modules less affected by pathological processes, which hit harder tasks requiring communication between different modules. We postulate that accomplishing an inhibitory task involving integrated and controlled processes requires efficient communication between different neural modules. This will make these inhibitory tasks more sensitive to the pathological process of Alzheimer's disease.

In support of the involvement of distributed damage in inhibitory failure in Alzheimer's disease, Bondi *et al.* (2002) found that different aspects of Stroop performance related to localized neurofibrillary tangles in temporal, parietal and frontal lobe structures in Alzheimer's disease patients. Further, Collette *et al.* (2002) report no link between inhibitory deficits in Alzheimer's disease patients (on the Stroop, Hayling, go-no go and cancellation tasks) and the presence of hypometabolism in the frontal lobes. They propose that inhibitory and other executive function deficits in Alzheimer's disease are better explained in terms of a

disconnection between anterior and posterior cortical regions than as a frontal lobe dysfunction.

There are some general issues in the assessment of inhibition that need to be addressed in future. Many inhibition measures are constructed difference scores that are very small in magnitude (e.g. Stroop, NP), and are likely to have very low reliability. Also, the high variability in the performance of Alzheimer's disease patients on most cognitive measures may swamp any mean group differences in performance. This means that it is difficult to draw strong conclusions about the presence or magnitude of effects of Alzheimer's disease on some of these inhibition indices. A further issue is the role of slowed processing on the effects of Alzheimer's disease on inhibition indices. In many paradigms, the inhibition condition is more complex than the control condition, so a general theory of slowed information processing in Alzheimer's disease would predict larger effects on the inhibitory task. From the review above, there is evidence that on three of the controlled inhibition tasks Alzheimer's disease effects are not caused by processing speed declines: (i) inhibitory deficits in the NP paradigm are unlikely to be caused by slow processing because there were no group differences in baseline naming latencies (Amieva *et al.*, 2002); (ii) a meta-analysis reveals substantially large Alzheimer's disease deficits on the interference relative to the baseline condition of the Stroop; and (iii) in the Hayling task there is no relationship between the inhibition index and a speed measure (Collette *et al.*, 1999a). Further direct investigation of this issue is needed but there is currently no evidence that slowed processing speed in Alzheimer's disease underlies effects on inhibition tasks.

## Conclusions

This review of the relatively few studies available in the field of Alzheimer's disease and inhibition leads to the conclusion that Alzheimer's disease has a strong effect on tasks requiring controlled inhibition processes, but relatively little effect on tasks requiring automatic inhibition. This conclusion needs to be tested in studies that systematically vary the controlled-automatic inhibitory load in the same group of patients. The underlying mechanisms of any Alzheimer's disease deficits in inhibitory tasks also need to be investigated to determine whether, for example, poor Stroop performance reflects a true inhibitory impairment or whether it reflects other factors, such as word-reading difficulties, problems with dual task performance or failure to understand task instructions.

One of the directions of future research may involve determining the fate of inhibitory processes in the course of Alzheimer's disease by means of longitudinal studies. In particular, it would be important to investigate how early the inhibitory decline is shown in comparison with episodic memory loss, generally considered to be the earlier marker of cognitive decline in Alzheimer's disease. Because inhibitory mechanisms are assumed to play a crucial role in orchestrating performance in various domains, such as perception, attention, memory and motor processes (Kok, 1999), know-

ing the different rates at which these multiple systems decline in Alzheimer's disease may considerably improve the theoretical and clinical knowledge of cognitive deterioration in Alzheimer's disease.

Further investigation of the implications of inhibitory dysfunction in Alzheimer's disease for behavioural problems during the disease course is also needed. For example, LeMarquand *et al.* (1998) present evidence of a link between inhibitory processing (as measured on the go-no go task) and behavioural problems in aggressive adolescents. It would be useful in future studies to know more about the link between cognitive and behavioural disinhibition in Alzheimer's disease.

Finally, the relationship of measures of inhibitory deficits in Alzheimer's disease with any changes in brain activation patterns or temporal patterns of evoked potentials is also a potential question of interest.

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