Running Title: Fluency in Alzheimer's disease: a meta-analysis

'Normal' semantic-phonemic fluency discrepancy in Alzheimer's disease? A meta-analytic study

Keith R Laws [1*], Amy Duncan [1], and Tim M Gale [1,2]

[1] *School of Psychology, University of Hertfordshire, UK*
[2] *Department of Psychiatry, QEII Hospital, HPFT, Welwyn Garden City, UK*

*Address for correspondence:

Professor Keith R Laws

School of Psychology

University of Hertfordshire

College Lane

Hatfield, Hertfordshire

AL10 9AB, UK

ABSTRACT

In a meta-analysis of 135 studies involving 6000 patients with Alzheimer's disease (AD) and 6057 healthy controls, we examined the relative degree of semantic and phonemic fluency impairment in AD patients. The effect size for semantic fluency (d= 2.10; 95%CI 2.22 to1.97) was significantly larger than for both phonemic fluency (d= 1.46: 95%CI 1.56 to 1.36) and picture naming (d= 1.54: 95%CI 1.66 to 1.40). In meta-regression analyses we found that studies with greater proportions of female patients and less severe dementia both led to better phonemic fluency; while perhaps surprisingly, increased patient education led to worse semantic fluency. Critically, in 50 studies measuring both semantic and phonemic fluency, the effect size for the semantic-phonemic discrepancy scores did not differ between AD patients and controls; and was unrelated to any of the moderator variables. The latter findings indicate that the semantic-phonemic fluency discrepancy measure often reported as an important distinguishing characteristic of AD patients may be an exaggerated normal tendency.

1. **Introduction**

Tests of verbal fluency are widely used to assess cognitive functioning following neurological damage and are viewed as sensitive indices of language dysfunction in Alzheimer's disease (AD). Depending on the type of fluency task, participants are asked to retrieve words that start with a specific letter (e.g. F, A, S: phonemic fluency) or words that belong to a semantic category (e.g. animals, clothing), typically, over a one-minute period. It has long been known that naming is impaired at an early stage in Alzheimer's disease (Bayles and Tomoeda, 1983; Martin and Fedio, 1983); however, this is true also of phonemic fluency (e.g. Adlam et al., 2006) and impaired semantic fluency has been viewed as a sign of early semantic degradation in presymptomatic AD patients (Chen et al., 2001), mild AD patients and those with Mild Cognitive Impairment (Adlam et al., 2006). Indeed, Adlam et al (2006) recently reported that semantic fluency was the only test of semantic functioning that significantly differentiated individuals with Mild Cognitive Impairment from healthy controls (see also Joubert et al, 2008; Murphy et al, 2006).

A key finding in the AD literature has been the documentation of a differentially greater semantic than phonemic fluency impairment and the associated neuropathological interpretation that flows from this finding (see Henry et al, 2004). It has been widely argued that category fluency is disproportionately impaired in AD, while phonemic fluency is usually more mildly impaired (e.g. Crossley, et al, 1997; Martin and Fedio, 1983; Monsch et al., 1994; Salmon et al, 1999) or even intact (Butters et al, 1987). The relatively greater impairment of semantic over phonemic fluency in AD has been used to differentiate AD from other dementias, for example, fronto-temporal dementia (Rascovsky et al., 2007) and to differentiate mild AD from healthy elderly subjects (e.g. Gomez and White, 2006). Nevertheless, the opposite pattern of worse phonemic fluency or comparable performance on

both measures of fluency has also been, albeit less frequently, reported (Hart et al, 1988; Nebes et al., 1984; Ober et al, 1986; Suhr and Jones, 1998). Heterogeneity on semantic and phonemic fluency tasks has been observed in AD patients. Indeed, Sherman and Massman (1999) reported that two thirds (n=145) of their patients showed the standard semantic disadvantage and one-third a phonemic disadvantage (n=72).

Several variables influence fluency in healthy participants, although not always consistently. Some have documented that phonemic and semantic fluency are inversely related to age (e.g. Phillips, 1999; Moreno-Martínez et al, 2008; Mathuranath et al, 2003). In a meta-analytic review, Rodriguez-Aranda and Martinussen (2006) reported that phonemic fluency declines slowly until the late 60s and then declines rapidly through the late 80s. The level of education is also important and typically leads to better fluency (e.g. Ardila et al, 2000; Mathuranath et al, 2003). Although consistent evidence indicates that education affects fluency, it is less clear if fluency across the lifespan varies as a function of education. In particular, education may be protective against age-associated decline in cognitive performance, as suggested by the concept of 'cognitive reserve' (Stern, 2002; Stern, 2003) and clearly, is something that lends itself to examination on fluency tasks. Indeed, since the early 1990's, a debate has waged concerning the relationship between education and cognitive decline in AD. In particular, some have surprisingly reported that better educated AD patients show faster cognitive decline (Amieva et al., 2005; Mortimer et al, 1991; Stern et al., 1999; Unverzagt et al., 1998), although others report slower cognitive decline in AD patients with higher education (Fritsch et al., 2002) and equivocal or no effects of education on rates of cognitive decline (Katzman et al., 1988; Wilson et al., 1988).

Another important influence on fluency is sex, though again, the findings in healthy participants have been mixed, with some reporting that women show better phonemic fluency than men (Bolla et al., 1990; Capitani et al, 1998; Crossley et al., 1997), while others report no sex difference (Borod et al., 1980; Gladsjo et al., 1999; Yeudall et al., 1986). In a large study of 1300 healthy individuals, Tombaugh et al (1999) found no sex differences for either phonemic or semantic fluency, though they did find that fluency was related to both age and education. Sex may also interact with fluency subcategory and in a study of 300 men and 300 women, Laws (2004) found that men outperformed women with tools and vehicles, while women performed better with fruits, but no sex difference emerged for animals (which is the most commonly used category – especially in studies of AD patients). A recent study examining a large number of semantic fluency subcategories in 28 male and 33 female AD patients found, that after controlling for dementia severity, male AD patients outperformed females in 13 of the 14 categories (Moreno-Martínez et al, 2008). Indeed, a somewhat neglected and perhaps surprising finding is that female AD patients manifest greater deficits on tasks of semantic memory. Several studies from the mid-90s showed that women have poorer performance on tasks of confrontation naming after controlling for the effects of age, education, duration of illness and AD severity (Buckwalter et al., 1993, 1996; Henderson and Buckwalter, 1994; Ripich et al., 1995). More recently, a meta-analysis of category-specific effects in AD patients (Laws et al, 2007) revealed that studies with higher proportions of females lead to worse naming in both categories. Critically, some evidence also reveals worse semantic, but not phonemic fluency in women (Henderson and Buckwalter, 1994; Ripich et al., 1995).

In this meta-analysis, we examine the role played by relevant moderator variables, including dementia severity (as measured by MMSE), age, sex, and education in predicting semantic

fluency, phonemic fluency and picture naming in AD patients, as well as their role in predicting the semantic-phonemic discrepancy– which have not been examined previously.

2. Method

Electronic searches for the words *'Alzheimer*'* AND *'fluency'* were entered into the Scopus and Web of Science search engines. Additionally, we obtained a list of studies contained in a previous meta-analysis from the first author of that study (Henry et al, 2004). The inclusion criteria were that the study presented means and standard deviations for semantic or phonemic fluency in patients with Alzheimer's disease and healthy controls (where available within those studies, we also derived picture naming data for analysis). This revealed 135 suitable studies published between 1983 and 2008. Data obtained from each study were converted into Cohen's *d* effect size (i.e. difference between the means for the patient and control groups divided by their pooled standard deviation). Effect sizes were weighted for variance to correct for upwardly biased estimation of the effect in small sample sizes (Rosenthal, 1991). All effect sizes were independently extracted, compared and verified by two of the authors. The nomenclature of Cohen (1988) suggests the following classification of Cohen's *d* effect sizes (small *d* = 0.20; medium *d* = 0.50; and large *d* = 0.80).

The meta-analysis was carried out using *MetaWin 2.1* (Rosenberg et al, 2000). When a significant index of heterogeneity was evident with a Fixed Effects Model, a Random Effects Model was employed (though it made no difference to the results reported). A Fixed Effects analysis assumes a single common effect (*d*) across all studies (i.e. no heterogeneity). In contrast, the Random Effects analysis allows the true effect in each study to be normally distributed (DerSimonian and Laird, 1986). This approach assumes random variation in the effect of interest among the studies. We also calculated a homogeneity statistic, Q_{wi} (Hedges

and Olkin, 1985), to test whether the studies can be taken to share a common population effect size. A significant Q_{wi} statistic indicates heterogeneity of the individual study effect sizes. To test for the significance of the mean effect, bias-corrected confidence intervals were calculated using bootstrapping with 999 replications (this approach does not require that effect sizes be parametrically distributed).

Some studies included more than one version of the same fluency task (e.g. animals and tools) and where this occurred, the individual effect sizes were pooled to produce an aggregated mean effect size (by far, the most common category was 'animals' and the most common letters were the standard 'FAS'). When studies included more than one patient group, to ensure the widest range of dementia severity, we selected the least impaired patient group as indicated, typically, by their Mini Mental State Examination scores (MMSE: Folstein et al., 1975). The 135 studies[1] provided a total of 6000 AD patients and 6057 healthy controls (Table 1 shows the demographic details for the AD patients and controls for each effect size). In the total sample, the AD patients and controls were closely matched for mean [SD] age (71.72[5.08] vs. 70.08[6.95]), and years of education (11.91[2.83] vs. 12.63[2.95]), although of course they did differ in MMSE scores (20.14[2.47] vs. 28.62[0.72]). The majority of studies included in the meta-analysis used National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's disease and Related Disorders Association (NINCDS/ADRDA: McKhann et al., 1984) criteria for diagnosing Alzheimer's disease.

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[1] This list of 135 studies and the list of 50 studies used for the discrepancy analysis are available on request from the first author

3. Results

A large weighted mean effect size for semantic fluency was derived from 92 studies (d= 2.10: 95%CI 2.22 to 1.97; unweighted d = 2.15). The semantic fluency studies were homogenous (Q_{wi} = 99.79, df = 90, p = .40). For Phonemic fluency, the mean effect size from 96 studies was large (d= 1.46: 95%CI 1.56 to 1.36; unweighted d = 1.47) and again, the studies were homogenous (Q_{wi} = 77.90, df = 95, p = .89)[2]. Finally, for picture naming, the mean effect size from 56 studies was also large (d= 1.54: 95%CI 1.66 to 1.40; unweighted d = 1.56); and the studies were homogenous (Q_{wi} = 63.65, df = 55, p = .20).

Insert Table 1 about here

Since the 95% confidence intervals for semantic fluency did not overlap with those for phonemic fluency and picture naming, the effect size for the former was significantly larger than the latter two (Julious, 2004). We made a further direct comparison of semantic and phonemic fluency effects sizes retrieved from the same subjects in 50 studies (see Appendix 2) involving large samples of AD patients (n=1771) and controls (n=2167); and thus controlled for potential individual differences in MMSE, age, education and gender ratio. We found that the effect size for semantic fluency was significantly greater than that for phonemic fluency (d=2.26 [95%CI 2.4 to 2.08] vs. 1.49[95%CI 1.6 to 1.35]: Q_B = 33.45, df = 1,98, p = .001, k=50).

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[2] The effect sizes for semantic and phonemic fluency closely accord with the r values of Henry et al (our d values convert to r= .72 and .59 respectively (Henry et al reported .73 and .55)

3.1 Moderator variables

A series of univariate weighted meta-regression[3] analyses were used to examine the impact of the following continuous variables (age, MMSE, education and proportion of females) on effect sizes. Table 2 shows that the proportion of female AD patients was a significant predictor of effect sizes for both phonemic (r=.33) and semantic fluency (r=.34), with the effect sizes being smaller in samples with more female patients. Although it failed just to reach significance, effect sizes for picture naming were larger in studies with greater proportions of female patients (r=-26). Dementia severity as measured by MMSE scores was a significant predictor of phonemic fluency (r=.37) and picture naming (r=.50) i.e. increasing MMSE scores and lower age led to reduced effects sizes; however, MMSE scores did not significantly predict semantic fluency scores (r=.20). Age predicted only picture naming (r=-.47). Finally, years of education significantly predicted only the effect sizes for semantic fluency (r=-.30) but, intriguingly, increased education led to increased effect sizes.

Insert Table 2 about here

3.2 Semantic-phonemic fluency discrepancy

Given the importance attached to the semantic-phonemic discrepancy in AD patients, effect sizes were calculated for this discrepancy in the AD patients and healthy controls separately. The discrepancy (i.e. semantic-phonemic) scores were derived from 50 studies described above. These analyses controlled for the specific type of fluency task employed. Surprisingly

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[3] We note that meta-regression uses group means as predictors (as opposed to individual subject performance) and thus may well reduce the degree of variability that exists for the predictor variable(s) across studies (see Thompson & Higgins, 2002) e.g. leading to potential false negatives.

perhaps, this analysis revealed discrepancy scores in AD patients and healthy controls that did not differ across the same 50 studies, with both showing commensurably better phonemic than semantic fluency ($d=$ .76 [95%CI 0.99 to 0.53]: vs. $d=$.78[95%CI 1.22 to 0.40])[4]; both samples were homogenous. Furthermore, the effect size for discrepancy in AD patients was highly correlated with the discrepancy for controls ($r=$.7, $p<$.0001). Figure 1 shows the funnel plots of the discrepancy scores for AD patients and controls. Funnel plots are a visual means for examining publication (and other) bias in meta-analysis. They are simple scatterplots of the effect size estimated from individual studies (x axis) against a measure of study size (y axis). In the absence of bias, results from studies with small sample sizes will scatter widely at the bottom of the graph, with the spread narrowing and closer to the mean among larger studies. It is clear from Figure 1 that although the means for AD patients and controls do not differ, the spread of scores is reduced in AD patients.

Insert Figure 1 about here

Finally, again we used univariate meta-regression analyses to examine the ability of the demographic variables to predict the discrepancy measure. None of the variables significantly predicted the discrepancy scores: MMSE ($Q_{wi} = 0.03$, $df = 1,34$, $p = .86$); age ($Q_{wi} = 0.44$, $df = 1,51$, $p = .50$); though proportion of female patients ($Q_{wi} = 3.16$, $df = 1,35$, $p = .07$) and education ($Q_{wi} = 3.2$, $df = 1,44$, $p = .07$) both approached significance. These findings indicate that the relative disadvantage for semantic over phonemic fluency occurs independently of dementia severity and patient age with possible weak links to education and the proportion of female patients.

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[4] Unweighted effect sizes were 0.76 vs. 0.79

4. Discussion

The current meta-analysis shows that AD patients are impaired on all three language-based tasks and as per the previous meta-analysis of Henry et al (2004), the effect size for semantic fluency (d= 2.10) was significantly greater than for either phonemic fluency (d= 1.46) or picture naming (d= 1.58). Critically and contrary to expectation, the effect size for the semantic-phonemic fluency discrepancy measure did not differ between AD patients and elderly controls. Using meta-regression analyses, we further explored the impact of four common moderator variables (proportion of female AD patients, MMSE scores, age, and education) on the effect sizes and for the semantic-phonemic discrepancy measure - these moderator effects are discussed in turn below.

Turning first to the role of sex, studies with a larger proportion of female AD patients produced smaller effect sizes both for semantic and for phonemic fluency. By contrast, the effect size for picture naming, although failing marginally to reach significance, was larger in studies with a greater proportion of female patients (cf. Laws et al, 2007). As noted, a few studies have documented greater semantic memory deficits in women with AD on naming tasks (Buckwalter et al., 1996; Henderson and Buckwalter, 1994; McPherson et al., 1999; Ripich et al., 1995) and semantic fluency, but not for phonemic fluency (Henderson and Buckwalter, 1994; Ripich et al., 1995). Given the large number of studies examined here, however, we would argue that the findings for fluency in this meta-analysis are robust. In other words, the tendency for women with AD to outperform men with AD may reflect a general tendency for healthy women to perform better than men on some, but not all linguistic tasks. Indeed, a surprising lack of clarity exists on how sex differences in healthy participants affect the performance of verbal tasks (see Wallentin, 2009); and further work is

required to determine on precisely which verbal tasks women outperform men and vice-versa.

We would naturally expect dementia severity (as measured by MMSE) to affect cognitive test performance generally in AD patients, and MMSE scores were indeed positively related to phonemic fluency and picture naming; however, they just failed to significantly predict semantic fluency. Although many findings show that deficits occur on all three tasks at early and even presymptomatic stages of the illness (e.g. Adlam et al., 2006; Chen et al., 2001; Martin and Fedio, 1983), unlike phonemic fluency and picture naming, the semantic fluency effect size does not become larger with worsening dementia. The current analyses suggest that semantic fluency is quite severely impaired early in the disease process and remains relatively stable while phonemic fluency and picture naming are initially less impaired, but continue to decline gradually with increasing dementia severity (at least in AD patients whose MMSE scores currently indicate mild to moderate dementia, i.e., a mean MMSE of 20). Indeed, semantic memory impairment is viewed as one of the earliest cognitive markers of AD, with the incidence in mild AD estimated at 50% (Hodges et al., 1992) and detectable even in Mild Cognitive Impairment cases (Adlam et al., 2006; Vogel et al., 2005). This early and severe semantic impairment may reflect how AD-related pathological changes affect different fluency tasks. An early and marked semantic fluency deficit is consistent with the presence of neurofibrillary tangles in the lateral temporal lobe region early in the course of AD (Braak and Braak, 1991, 1996). By contrast, phonemic fluency is more commonly observed later in the course of the illness and is thought to reflect the extent to which neuropathology impacts the left prefrontal and inferior parietal cortex (Abrahams et al., 2003; Gourovitch et al., 2000; Keilp et al., 1999; Mummery et al., 1996). Semantic fluency is known to recruit both frontal and temporal lobe regions (Gourovitch, Kirkby, and Goldberg,

2000; Hirono et al., 2001; Kitabayashi et al., 2001; Mummery et al, 1996; Pihlajamaki et al., 2000). Deficits on tests of semantic fluency may therefore reflect problems with semantic memory in addition to, or instead of executive dysfunction. Given the different neuro-anatomical substrates associated with semantic and phonemic fluency, the relative pattern of semantic and phonemic fluency may provide important insights into the neurological basis and progression of Alzheimer's disease.

Intriguingly, increased educational attainment led to greater semantic fluency impairment, but had no significant impact on phonemic fluency or picture naming. Studies of AD patients largely attempt to match the patients and healthy controls for educational attainment as far as possible; and so, higher functioning controls tend to deviate much more from their matched AD patients than less well-educated participants. As noted, greater education in AD patients has been associated with faster cognitive decline (Amieva et al., 2005; Mortimer et al, 1991; Stern et al 1999; Unverzagt et al., 1998). Variability in findings relating to education have been linked to the notion of 'Cognitive Reserve' (CR) i.e. the hypothesised capacity of the brain to actively compensate for brain injury or even the normal effects of aging (Stern, 2002). A greater CR is hypothesized to be a protective factor that raises the threshold for the manifestation of cognitive deficits (and clinical symptoms); while a lower CR is viewed as a vulnerability factor (Satz, 1993). Hence, greater CR has been associated with an apparently more rapid cognitive decline in AD patients (Scarmeas et al., 2006; Stern et al., 1999) because, at some point, AD pathology becomes too severe to support the processes that mediate CR. In the case of semantic fluency, CR appears to offer one possible interpretation i.e. that in the better-educated patients, semantic fluency holds-up until some critical point – at which a more catastrophic decline occurs. This may also accord with the lack of an associated decline in semantic fluency and dementia severity i.e. semantic fluency may

decline in a stepwise rather than linear manner. Whereas for phonemic fluency and picture naming, the reverse profile emerges i.e. AD patients show a gradual linear decline associated with dementia severity, but little relationship with education. Indeed, some work indicates that precise relationship between education and cognitive decline in AD does appear to be moderated somewhat by task (Scarmeas et al., 2006).

Surprisingly, little normative data exist for the semantic-phonemic discrepancy scores in healthy subjects, although Gladsjo et al (1999) did report that both large phonemic and large semantic discrepancies were 'not uncommon' in their sample of 768 healthy individuals. While semantic fluency is often reported to be more impaired than phonemic fluency in AD, the same effect has occasionally been observed in normal healthy ageing (Crossley et al., 1997; Kozora and Cullum, 1995; Tomer and Levin, 1993). Nonetheless, little is known about whether AD patients show greater variability than healthy participants. The data reported here, however, did permit an estimate of the effect size for semantic-phonemic discrepancy scores from large samples of controls (n=2167) and AD patients (n=1771) from exactly the same 50 studies and critically, using the same materials (categories and letters, testing conditions and so on). This analysis revealed that the mean discrepancy effect size for AD patients was almost identical to that of healthy controls, with both showing large effects ($d=$ .74 vs. $d=$.75). Furthermore, the discrepancy effect size in healthy controls strongly predicted the discrepancy in AD patients.

We note, however, that the profiles are not parallel since the spread of difference scores is attenuated in AD patients (at both ends of the tails i.e. there are fewer extreme advantages for semantic or phonemic fluency). Heterogeneity on semantic and phonemic fluency tasks has been observed in AD patients. Indeed, Sherman and Massman (1999) reported that two thirds

of their patients showed the standard semantic disadvantage and one-third a phonemic

disadvantage. Several previous studies have proposed a subtype of AD, where the disease

appears to show a 'frontal' manifestation initially rather than the more typical temporal

presentation (Braak and Braak, 1991, 1996); and therefore, AD patients who display poorer

phonemic than semantic fluency may be displaying this more prominent frontal dysfunction

(Hinkin et al., 1995; Soininen et al., 1995). In the current meta-analysis, for approximately

76% (38/50) of the studies, AD patients showed the predicted pattern of better phonemic than

semantic fluency. In control samples, a more even split emerged with 60% (n=30) of studies

documenting better phonemic than semantic fluency and 40% (n=20) showing the reverse

(see Figure 1). Although AD patients exhibit a more consistent semantic fluency advantage

than healthy elderly controls, both groups show the same mean degree of semantic advantage.

Hence, the poorer semantic than phonemic fluency so often reported in AD samples, appears

to reflect a profile present in healthy subjects (albeit with greater variability). This must cast

doubt on notions that greater semantic relative to phonemic fluency in AD necessarily

reflects the differential impact of the disease on temporal lobe-based semantic knowledge

systems; or in some way, may distinguish AD patients from controls or other even possibly

pathologies. These conclusions appear also to be underpinned by the fact that the advantage

for phonemic over semantic fluency in AD exists along the continua of dementia severity,

age, education and regardless of patient sex.

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Table 1. Demographic information for the Alzheimer's (AD) patients and the controls for each task

Test	K	Sample size		MMSE		Age		Education		Proportion females		Effect size
		AD	Controls	AD	Controls	AD	Controls	AD	Controls	AD	Controls	d
Semantic Fluency	92	4611	4620	20.0	28.6	72.2	69.9	11.6	12.0	.58	.59	2.10
Phonemic fluency	96	3111	3525	20.3	28.8	72.2	70.3	12.2	13.1	.57	.57	1.46
Picture naming	56	2607	2285	19.6	28.8	71.2	70.8	12.2	13.0	.56	.57	1.54

Note. K = the number of studies

Table 3. Mean [SD] demographics for AD patients and controls in 50 studies measuring both semantic and phonemic fluency

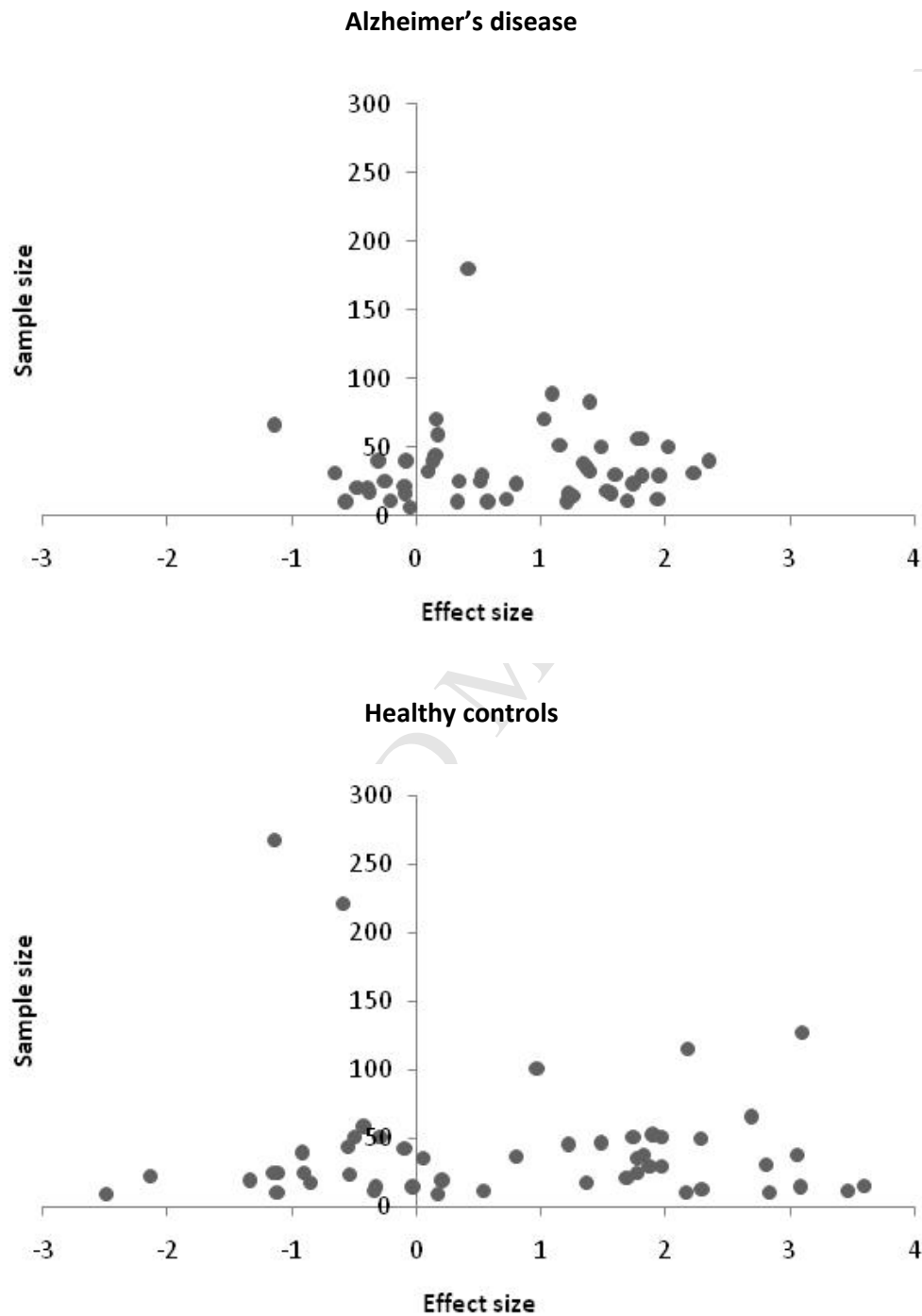| Group	K	Sample size [range]	MMSE	Age	Education	Proportion females	Effect size [range]
AD	50	1771 [6 to 180]	20.2 [2.5]	72.8 [3.8]	12.5 [2.5]	.57 [.17]	-0.75 [-2.3 to 1.1]
Controls	50	2167 [10 to 267]	28.7 [.55]	70.1 [7.2]	13.0 [2.3]	.56 [.15]	-0.74 [-3.6 to 2.5]

Note. *K* = the number of studies

Table 2. Meta-regression analyses for moderator variables

Moderator variable	Semantic	Phonemic	Picture naming
MMSE	$Q_{1,57}=3.3,\ p=.07$	$Q_{1,64}=10.8,\ p<.001$	$Q_{1,33}=15.2,\ p<.001$
Years of education	$Q_{1,73}=12.5,\ p<.001$	$Q_{1,72}=1.6,\ p=.69$	$Q_{1,38}=0.9,\ p=.66$
Proportion of female patients	$Q_{1,60}=8.1,\ p=.004$	$Q_{1,65}=9.4,\ p=.002$	$Q_{1,37}=2.9,\ p=.09$
Age	$Q_{1,85}=1.1,\ p=.28$	$Q_{1,91}=0.3,\ p=.56$	$Q_{1,50}=14.5,\ p<.001$

Figure 1. Funnel plots displaying effect sizes for the semantic-phonemic discrepancy in AD patients and healthy controls (derived from the same 50 studies)

Note. phonemic better than semantic fluency (-); semantic better than phonemic fluency (+)