

Semantic inhibition and dementia severity in Alzheimer's disease

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Abstract

Background: Semantic inhibition is often found to be impaired in Alzheimer's disease (AD). The sentence completion task (Hayling test) was used to investigate whether it would be useful for differentiating mild AD from moderate AD. **Method:** Latency responses and error scores in the automatic and inhibition parts of the test were registered in these two groups of patients and in a group of healthy older participants. The types of errors were also analysed. Group differences were analysed by ANOVA. In addition, relationships with other neuropsychological tests were reported. **Results:** Participants with moderate AD performed worse than controls in both the automatic and inhibition sections, whereas participants with mild AD exhibited impaired performance in the inhibition part, but not in the automatic part. Differences between the groups with mild and moderate AD appeared only in the error scores in the inhibition part, specifically type 3 errors. Error scores in the inhibition part correlated with performance in verbal fluency and working memory tests. **Conclusions:** The Hayling task may be a useful tool for investigating control of inhibition in different stages of AD because different patterns of responses were observed.

Keywords: Semantic inhibition, dementia, Alzheimer's disease, executive functions, Hayling task.

Resumen

Inhibición semántica y enfermedad de Alzheimer con diferentes grados de severidad. Antecedentes: los déficits en inhibición semántica en personas con enfermedad de Alzheimer (EA) son frecuentes. La tarea de completamiento de frases de Hayling se utilizó para determinar si ésta podría ser útil para diferenciar EA leve de EA moderado. **Método:** se compararon los tiempos de respuesta y el número de errores obtenidos en las partes automática e inhibición en los dos grupos de pacientes y en adultos mayores sanos. El tipo de errores fue también analizado. Las diferencias entre los grupos fueron analizadas mediante ANOVA. Además se obtuvieron las correlaciones con otros tests neuropsicológicos. **Resultados:** los pacientes con EA moderado mostraron peor ejecución en las dos partes: automática e inhibición, mientras que el grupo EA leve mostró déficits solo en inhibición. Los grupos leve y moderado se diferenciaron en el número de errores en inhibición, específicamente en errores tipo 3. El número de errores en inhibición correlacionó con fluencia verbal y memoria de trabajo. **Conclusiones:** la tarea Hayling podría ser útil para investigar control inhibitorio en diferentes etapas de la EA ya que se observaron diferentes patrones de respuesta.

Palabras clave: inhibición semántica, demencia, enfermedad de Alzheimer, funciones ejecutivas, tarea Hayling.

It is well known that Alzheimer's disease (AD) is primarily diagnosed by episodic memory failures, often associated with emotional deficits (Melendez et al., 2019). In recent decades research in the neuropsychological field indicates that the second most important symptom of the early manifestation of AD is a decrease in executive functioning (EF) (Perry, Watson, & Hodges, 2000). EF could be defined as a set of "cognitive skills that are responsible for planning, initiation sequencing, and monitoring of complex goal-directed behaviours" (Royal et al., 2002). EF is a multicomponent construct that can be measured by a variety of neuropsychological tests.

Control of inhibition seems to be more impaired than other executive functions in people with AD (e.g. Amineva, Philips, Della Sala, & Henry, 2004). Some studies have shown that inhibition impairment is present early in AD and increases gradually (Belànger

& Belleville, 2009). The results of a recent meta-analysis using a variety of tasks have indicated inhibitory control impairment in AD, with dementia severity being an important contributing factor in these deficits (Kaiser, Kuhlman, & Bosnjak, 2018). Control of inhibition plays an important role in tasks that require the suppression of automated well-learned responses, and it is necessary when the individual undertakes a novel task or a task that has to be done in a different way. This ability has traditionally been evaluated using the verbal fluency and Stroop tests. However, the use of these tests has received some criticism. For instance, some authors have warned about a possible lack of ecological validity (Burgess et al., 2006; Martyr, Boycheva, & Kudlicka, 2017) because the performance on these tests shows only a modest association with everyday functioning in people with AD. Instead, these authors proposed the use of the Hayling sentence completion test (Burgess & Shallice, 1996), which has a closer resemblance to the inhibition demands of real life (for instance, in conversations or other social interactions). Another advantage of this test is that it is easy to administer, it takes no more than 10 minutes to complete, and individuals with motor or visual difficulties can perform the task.

In the Hayling task the individual is asked to complete 30 sentences with the last word missing. In part 1 (automatic), the

word is strongly constrained by the preceding context, (eg., in the sentence “This man has travelled everywhere around the ...”, the correct response would be “world”). In part 2 (inhibition) the individual must give a word that makes no sense in the sentence context or is unrelated to the target word. For instance, for the sentence “Most sharks attack very close to the...”, the participant could give the word “table”. Thus, in order to accomplish this task, the individual has to inhibit the most obvious word that fits in the sentence context (“coast”) and generate a new unrelated word. In both sections, the number of errors and the response time (RT) are registered. In this task, the error scores are calculated by combining type 1 (when the participant completes the sentence with a word somewhat related to the target word) and type 3 errors (when the individual produces a word that fits the sentence when instructed to produce a word irrelevant to the sentence context) following the classical procedure of giving 1 point to type 1 errors and 3 points to type 3 errors (Burgess & Shallice, 1996). If a subject cannot respond within 60 seconds, this response is considered as type 3 error and 60 seconds is recorded as the latency response. If a subject cannot respond on more than one item the test is considered not appropriated for this individual (as per test manual) and was excluded from the study.

In spite of the interest in the use of the Hayling test in people with AD, the number of related studies is still quite low. Moreover, most of the existing studies used participants with a wide range of dementia severity (mild-to-moderate, Collette, Van der Linden, & Salmon, 1999; Belànger & Belleville, 2009; Belleville, Rouleau, & Van del Linden, 2006, 2007). Another study by Martyr et al., (2017) used early-stages AD participants with the aim to find possible differences between people with AD and people with Parkinson’s disease.

The present study investigates semantic inhibition impairment in people with AD, but our aim was to compare mild and moderate stages of AD and to find possible different patterns of deterioration depending on the disease severity. Although the clinical course of AD is gradual, it is useful to distinguish different AD severity levels in order to better understand its progression and develop intervention strategies adapted to each individual. We hypothesized that participants with mild AD would perform quite well on the automatic section but have more difficulties on the inhibition section of the test (compared to healthy controls), whereas the performance of people with moderate AD would be deficient on both parts of the test. We also expected that mild and moderate participants would differ more on type 3 errors (reflecting total failure to inhibit the target word) than on type 1 errors (reflecting partial inhibition deficits). Finally, the associations between the Hayling test measures and other neuropsychological tests routinely used to evaluate dementia in these patients were also examined in this study with the aim to determine which measures of the Hayling task were related to other tests of executive functioning and working memory. We hypothesize that the inhibition part of the test is more related to other cognitive measures than the automatic part. To our knowledge, very few studies have explored this issue.

Method

Participants

The final sample consisted of 31 individuals with AD (15 individuals with mild AD, and 16 individuals with moderate AD).

In addition, a sample of 15 healthy elderly individuals made up a control group. They were diagnosed according to the NINCDS-ADRDA criteria (McKhann et al., 1984) and the *Diagnostic and Statistical Manual for Mental Disorders-Fourth Edition (DSM-IV)* criteria for dementia of the Alzheimer type (American Psychiatric Association, 1994). The two groups were differentiated according to the severity of the illness, mild and moderate, on the basis of the Clinical Dementia Rating scale (CDR, Hughes, Berg, Danziger, Coben, & Martin, 1982). None of them presented clinical symptoms of depression (based on the short version of the Geriatric Depression scale by Yesavage et al., 1984) or other psychiatric disorders. The two groups of AD patients did not differ from the control group in age or years of education. Participants or their relatives gave their written informed consent, which was approved by the institutional review boards of the University.

Instruments

The material consisted of 30 sentences randomly distributed in two parts, automatic and inhibition, with 15 sentences in each part, and 4 sentences used as practice sentences (Table 1). The sentences of the present study had a cloze probability of between 97 and 100% (previously determined on a sentence completion task performed by a group of 189 university students), and the final words (key words) had frequency of occurrence per million values ranging from 24 to 334 and subjective ratings of familiarity ranging from 4.4 to 6.7 according to the EsPal database (Duchon, Perea, Sebastián-Gallés, Martí, & Carreiras, 2013). It should be noted that although Pérez-Pérez et al., (2016) developed a Spanish version of the Hayling task for evaluating healthy individuals, when the present study was conducted this study had not been published yet.

Procedure

All the participants were tested individually in a quiet room. In the first session, they completed the neuropsychological tests. They included a general screening cognitive test (Mini-Mental State examination, MMSE by Folstein, Folstein, & McHugh, 1975), a vocabulary test (Boston Naming Test, BNT by Kaplan, Goodglass, & Weintraub, 2001, 12-item version by Serrano, Allegri, Butman, Nagle, & Ranalli, 2001), and classical measures of verbal inhibition (phonological and semantic fluency) and working memory capacity (WM) (word span, alphabetical span, digit span forward, digit span backward and direct and reverse Corsi blocks tasks). In the second session, the participants were presented with the Hayling task. The instructions, procedure, and scoring were the same as in the original test by Burgess and Shallice (1996).

Data analysis

To compare the performance of the three groups on the Hayling test, we conducted two ANOVAs: (a) a mixed 3×2 ANOVA, with the RTs as dependent variable, and two independent variables (Group as a between factor: control, mild AD, and moderate AD, and Condition: automatic and inhibition as a within factor); and (b) the same design was used with the error scores as dependent variable. In case of interaction, post hoc simple effects tests and *t* tests pairwise comparisons with Bonferroni correction were performed when needed. The level of significance was set at *p*

Table 1
List of sentences of the Hayling task

Automatic section	Inhibition section
Practice sentences: Hay que tostar el pan por ambos LADOS (You have to toast the bread on both SIDES) Cada día desayuno un café con LECHE (I have coffee with MILK for breakfast every day)	Practice sentence: Ella lleva el anillo puesto en el DEDO (She's wearing the ring on her FINGER) Las plantas se secarán si no tienen AGUA. The plants will dry out if they don't have WATER
Test:	Test:
1. Se saludaron dándose la MANO (They greeted each other by shaking HANDS)	1. El abuelo cuida de su NIETO (The grandfather takes care of his GRANDSON)
2. Él tiene sólo 9 años, todavía es un NIÑO (He's only 9 years old. He's just a CHILD)	2. Para leer necesito ponerme las GAFAS (I have to put my GLASSES on to read)
3. Se pincharon las cuatro ruedas del COCHE (All four tires on the CAR were flat)	3. Los católicos van los domingos a MISA (Catholics go to MASS on Sunday)
4. La gallina pone HUEVOS (The hen lays EGGS)	4. Con la cámara hago una FOTO (I use the camera to take a PHOTO)
5. El pájaro estaba dentro de la JAULA (The bird was inside the CAGE)	5. A la hora de comer nos sentamos todos a la MESA (When it's time to eat, we sit at the TABLE)
6. Entró cuidadosamente en la habitación sin hacer RUIDO (He entered the room carefully without making NOISE)	6. La comida se sirve en un PLATO (Food is served on a PLATE)
7. En otoño, de los árboles caen las HOJAS (In autumn, trees lose their LEAVES)	7. Se bebió una copa de VINO (He drank a glass of WINE)
8. Me pongo el anillo en el DEDO (I am putting the ring on my FINGER)	8. Con la llave abro la PUERTA (I use the key to open the DOOR)
9. No puedo entrar en casa si no tengo la LLAVE (I can't get in the house if I don't have the KEY)	9. Para coser necesitas aguja e HILO (You need a needle and THREAD to sew)
10. Cojo el paraguas porque han anunciado LLUVIA (I'm taking the umbrella because they said it was going to RAIN)	10. Me acuesto en la CAMA (I lie down on the BED)
11. Nadie ha limpiado y está todo muy SUCIO (Nobody has cleaned up, and everything is very DIRTY)	11. Me siento en una SILLA (I sit down on a CHAIR)
12. En el mar nadan los PECES (FISH swim in the sea)	12. El capitán es el último en abandonar el BARCO (The captain is the last one to leave the SHIP)
13. Cuando hace buen día el cielo es de color AZUL (When it's a nice day, the sky is the color BLUE)	13. Fui al dentista porque me dolía un DIENTE (I went to the dentist because my TOOTH hurt)
14. El come demasiado y está muy GORDO (He eats too much and is quite FAT)	14. Un perro tiene cuatro PATAS (A dog has four PAWS)
15. No puedo andar porque me he roto una PIERNA (I can't walk because I broke my LEG)	15. No sale agua aunque he abierto el GRIFO (I turned on the FAUCET, but no water comes out)

< 0.05. The effects sizes were calculated by means of Eta square (η^2). Finally, a matrix of product-moment Pearson correlations was computed to determine the relationship between the measures on the Hayling task and the performance on the neuropsychological tests. The IBM SPSS 24.0 version was used for all the statistical analyses.

Results

Mild and moderate AD groups showed significant deficits on all the neuropsychological tests, except for the Corsi cubes test (inverse), where only the participants with moderate AD were deficient (Table 2). Regarding the performance on the Hayling test, response times on the Hayling task are presented in Table 3, which shows that RTs were slower for the two groups of individuals with AD than for controls; in turn, people with moderate AD were slower than those with mild AD. The statistical analysis revealed significant effects for Group ($F(2,43) = 10.28, p < 0.01, \eta^2 = 0.32$),

Condition ($F(1,43) = 68.23, p < 0.01, \eta^2 = 0.61$), and the interaction ($F(2,43) = 9.28, p < 0.01, \eta^2 = 0.30$). In order to study this interaction, simple effect tests for each condition between groups, and post-hoc comparisons with Bonferroni correction were performed. The simple effects test showed significant differences between groups for the automatic condition ($F(2,43) = 6.98, p < 0.05, \eta^2 = 0.24$), with longer latency responses in the moderate AD group than in the control group ($p < 0.05$). However, there were no significant differences between controls and mild AD and between mild and moderate AD. The simple effects tests also showed significant differences between groups for the inhibition condition ($F(2,43) = 9.84, p < 0.01, \eta^2 = 0.31$) with longer latency responses for mild AD than for the control ($p < 0.01$), moderate AD than control ($p < 0.01$), and moderate than mild AD groups ($p < 0.01$). Thus, both AD groups differed from the controls in the inhibition condition but, in the automatic condition, only moderate AD differed from the controls. Mild and moderate AD groups did not differ in the automatic or the inhibition conditions.

Regarding the study of each group, the *t* test with Bonferroni correction showed significant effect of the condition in the control group ($t(1,14) = -5.83, p < 0.01$) in the mild AD group ($t(1,15) = -5.90, p < 0.01$) and in the moderate AD group ($t(1,14) = -5.01, p < 0.01$) with longer latency responses in the inhibition condition than in the automatic condition in the three cases.

Regarding the error scores, Table 3 shows higher error scores on the inhibition part of the test than on the automatic part, and the difference was greater in the participants with AD than in the control group. The statistical analysis showed significant effects for Group ($F(2,43) = 28.27, p < 0.01, \eta^2 = 0.57$), Condition ($F(1,43) = 37.32, p < 0.01, \eta^2 = 0.46$), and the interaction ($F(2,43) = 11.80, p < 0.01, \eta^2 = 0.35$). In order to examine the interaction, the simple effects test of each condition between groups showed significant differences between groups for automatic condition ($F(2, 43) = 3.27, p < 0.05, \eta^2 = 0.13$), with a greater number of errors in the moderate AD than in the control group ($p < 0.05$), but there were no significant differences between controls and mild AD and between mild and moderate AD. The simple effects tests also showed significant differences between groups for the inhibition condition ($F(2,43) = 23.02, p < 0.01, \eta^2 = 0.52$) with a greater number of errors in the moderate AD group than in the controls ($p < 0.01$), in the mild AD group than in the controls ($p < 0.01$), and in the moderate AD than in the mild AD participants ($p < 0.01$).

Thus, The error scores of the two groups of participants with AD (mild and moderate) differed from the control group in the inhibition condition, but in the automatic condition, only moderate AD differed from controls. Mild and moderate AD groups did not differ in the automatic condition, but they did in the inhibition condition. Considering the number of type 1 errors in the inhibition condition, the one-way ANOVA with Group as a between factor showed significant differences for Group ($F(2,43) = 13.42, p < 0.01, \eta^2 = 0.38$). Post-hoc analysis showed significant differences between controls and mild AD ($p < 0.01$) and between controls and moderate AD ($p < 0.01$), but not between mild and moderate AD groups. Considering the type 3 errors, there were significant effects of Group ($F(2,43) = 11.35, p < 0.01, \eta^2 = 0.35$), and the post-hoc test revealed significant differences between controls and moderate AD ($p < 0.01$) and between mild and moderate AD groups ($p < 0.01$), but not between controls and mild AD groups. Thus, the moderate AD group differed from controls on both types of errors but the mild AD group differed from controls only on type 3 errors. Thus, mild and moderate AD groups differed on type 3 errors but not on type 1 errors.

Regarding the relationship between the performance on the Hayling test and the other neuropsychological tests in people with AD, significant negative relationships were found between the RTs in the automatic condition and the semantic and phonemic fluency tests ($p < .05$), between the RTs in the inhibition condition and the semantic fluency ($p < .05$), digit span ($p < .01$), digit ordering ($p < .01$), Corsi direct ($p < .01$) and Corsi inverse tests ($p < .01$), and between the error scores on the inhibition section and the semantic fluency ($p < .05$) and alpha span ($p < .05$). The error scores in the automatic condition only showed significant relationships with digit ordering ($p < .05$). The full correlation matrix is shown in Table 4.

Discussion

This study examines the use of the Hayling test to differentiate dementia severity in people with AD. People with AD presented worse performance in the inhibition condition than in the automatic condition of the Hayling test, as expected based on previous studies using participants with mild-to moderate AD (Belleville et al., 2006; Belanger & Belleville, 2009; Collette et al., 1999). However, the present study aimed to discover whether some of the measures on the Hayling test could differentiate people with mild AD from people with moderate AD. The results revealed that the mild and moderate AD participants did not show the same pattern of performance on the Hayling task. Mild AD participants only showed impairment on the inhibition part of the test, whereas moderate AD participants showed impairment on both the automatic and inhibition parts.

Thus, the present study shows that initiation and suppression abilities are impaired differently in people with AD depending on the AD severity. Well-learned and automated responses might still be preserved in the initial phase of AD, but not in posterior phases. The Hayling test would be an appropriate measure to differentiate between these two cognitive capacities (compared to more traditional inhibitory control tests such as Stroop or verbal fluency tests, which do not make this distinction), and it could be used by clinicians and researchers to better understand the neuropsychological profile of AD in each stage.

Regarding the error responses (type 1 and type 3), in the present study, people with moderate AD differed from healthy controls

Table 2
Demographic and neuropsychological data of the participants

Test	Control M (SD)	Mild AD M (SD)	Moderate AD M (SD)
Age	77.9 (5.14)	79.1 (6.26)	79.3 (3.16)
Gender (M/F)	8/8	7/8	8/8
Education (years)	10.57 (4.12)	11.2 (3.85)	8.66 (3.89)
MMSE	28.66 (2.49)	23.81 (0.91)**	22.46 (1.06)**
BNT	10.86 (0.35)	9.68 (0.79)**	9.13 (0.74)**
Semantic fluency	16.46 (2.47)	13.28 (3.64)**	8.80 (3.55)**
Phonemic fluency	16.00 (1.41)	9.78 (2.66)**	7.10 (1.44)**
Word span	4.33 (0.48)	4.11 (1.16)**	3.70 (8.84)**
Alpha span	3.46 (0.51)	3.35 (0.49)*	2.80 (0.78)**
Digit span	5.69 (0.63)	4.21 (1.18)**	4.40 (0.51)**
Digit ordering	3.46 (0.51)	3.07 (0.47)**	2.40 (1.42)**
Corsi cubes direct	6.84 (0.55)	3.85 (0.66)**	3.20 (1.68)**
Corsi cubes inverse	4.07 (0.49)	3.28 (1.12)	3.10 (1.66)*

Notes: AD = Alzheimer's disease. Mild AD and moderate AD groups were compared with the older control group (Tuckey test after ANOVA). The differences between mild and moderate AD were only significant ($p < .001$) for the alpha span test. MMSE = Mini-Mental State examination BNT = Boston Naming Test
** $p < .01$, * $p < .05$

Table 3
Descriptive data of participants in the performance on the Hayling test

	Controls	Mild AD M (SD)	Moderate AD M (SD)
RT Automatic	0.88 (0.45)	1.11 (0.18)	1.45 (0.55)
RT Inhibition	2.38 (0.66)	1.11 (0.18)	1.45 (0.55)
Errors Automatic	0.07 (0.26)	1.19 (1.51)	2.53 (4.36)
Errors Inhibition	0.67 (0.48)	6.06 (2.05)	14.00 (9.54)
Type 1	0.07 (0.26)	0.37 (0.50)	1.28 (2.62)
Type 3	0.20 (0.41)	3.87 (2.78)	4.00 (2.77)

Note: AD = Alzheimer's disease, RT = response time

Table 4
Matrix of correlations between Hayling measures (H) and neuropsychological tests

Measures	1	2	3	4	5	6	7	8	9	10	11	12
1. RT Automatic H	–	.46**	.41*	.35*	.39*	.41*	-.08	.11	.03	-.32	-.05**	-.69
2. RT Inhibition H		–	-.07	-.04	-.47*	-.26	-.12	.17	-.59**	-.71**	.70**	-.75**
3. Error score Automatic H			–	.03	.34	.01	.17	.26	.33	-.37*	.18	.24
4. Error score Inhibition H				–	-.43*	-.29	-.28	-.39*	-.01	-.41	-.48	-.21
5. Semantic fluency					–	.44*	.56*	.08	.47*	.57**	.40*	.21
6. Phonemic fluency						–	.44*	.10	.05	.41*	.40*	.21
7. Word span							–	.21	.59**	.02	.10	.03
8. Alpha span								–	.04	.07	.10	.11
9. Digit span									–	.23	.29	.36
10. Digit ordering										–	.85**	.68**
11. Corsi cubes (direct)											–	.86**
12. Corsi cubes (inverse)												–

* p < .05, **p < .01

on both types of errors, which can be interpreted as a complete failure to inhibit the word that fits the sentence. This result agrees with the results by Collette et al. (1999, 2002) and Belànger and Belleville (2009), who found more type 3 errors in people with AD than in healthy older people. The mild AD group differed from the control group on type 1 errors, but not on type 3 errors, which can be interpreted as partial inhibition difficulties rather than complete failure. This result did not completely agree with the findings by Martyr et al., (2017) showing more type 3 errors in AD participants in the early stages than controls. Some differences in the scoring procedure (that study used did not use the standard test scoring protocol) might explain in part these differences.

In the present study, performance on the Hayling test (especially on the inhibition part) correlated with other measures of executive functioning such as semantic fluency and working memory. The relationship with semantic fluency is consistent with results from studies showing more impairment in semantic fluency than in phonemic fluency in people with AD (e.g. Henry, Crawford, & Phillips, 2004, for a meta-analysis). In addition, a decline in WM in people with AD is also frequently observed (Baddeley, Logie, Bressi, Della Sala, & Spinnler, 1986), although its relationship with inhibitory control, measured by the Hayling task, has only been explored in healthy older individuals (Borella, Ludwig, Fagot, &

de Ribaupierre, 2011). The authors obtained results supporting the hypotheses that older individuals with higher WM capacity can maintain a large amount of information active, and that they are more efficient in resisting interference (Sebastian & Mediavilla, 2017). The results of the present study with participants with AD would agree with these hypotheses.

The findings from the present study suggest that the Hayling sentence completion test may be a valuable tool to help clinicians and researchers to assess inhibitory control in people with different degrees of AD severity, offering a different approach from more widely used tests. The results of the present study also suggest that mild and moderate levels of dementia in people suffering from AD can be explored by analysing the errors on the inhibition part of the test. The present study can be considered a first step, and more data are needed to better understand the characteristics and progression of the inhibitory difficulties in people with AD, for instance, with larger sample sizes and through longitudinal studies.

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