

Development of a Neuropsychological Test to Evaluate Cognitive Flexibility

Shinya Takeda* and Toshiki Fukuzaki*

*Department of Clinical Psychology, Tottori University Graduate School of Medical Sciences, Yonago 683-8503, Japan

ABSTRACT

Background Cognitive flexibility is also referred to as set-shifting and is considered to be an important activity of the frontal lobe. The objective of this study was to produce a Cognitive Flexibility Test (CFT) that can evaluate cognitive flexibility in a short time and in a simple manner and to verify the usefulness of the test.

Methods The CFT, Mini Mental State Examination (MMSE), Verbal Fluency Test (VFT), and Geriatric Depression Scale 15 (GDS-15) were implemented among a total of 94 elderly people who live at home. An “A” version of CFT (CFT-A), which asked about the possible uses of a plastic bottle other than drinking and a “B” version (CFT-B), which asked about the possible uses of a ballpoint pen other than writing, were produced.

Results In the case of CFT-A, after adjusting the number of years of education, a significant correlation was found between CFT-A and the variables age, VFT, and MMSE. As for CFT-B, after adjusting the number of years of education, it was found to have a significant correlation with age and VFT. The number of responses for CFT-A and CFT-B were significantly lower than that of VFT. The number of responses for CFT-B was significantly lower than that of CFT-A.

Conclusion The CFT-A may be useful as a neuropsychological test to evaluate cognitive flexibility among elderly people that can be implemented easily in a short time.

Key words cognitive flexibility; Cognitive Flexibility Test; elderly people; neuropsychological test

The population of elderly people is increasing globally, and it is expected that the percentage of elderly people aged 60 or above will be 22% by 2050.¹ Due to such demographic changes, it is expected that there will be a global increase in dementia, for which aging is the greatest risk factor.² In fact, the World Health Organization has reported that globally, the number

of patients with dementia has been increasing rapidly in recent years.³ The prevalence of dementia doubles approximately every six years after the age of 65, going from 7% between ages 75–79 to 12% between ages 80–84, 20% between ages 85–89, and 40% at age 90 or above.⁴ While dementia causes a general disabling of cognitive functions, the cognitive functions that are disabled vary according to the disease type in the initial stage. Although there is currently no total cure for dementia, because of the popularity of drugs such as Donepezil Hydrochloride, early-stage detection likely delays progress and improves symptoms.⁵ Hence, there is an urgent demand for the development and deployment of high-sensitivity measurement methods that can detect cognitive functional impairment as seen in the early stages of all types of dementia.⁶

In the cerebral cortex, which controls cognitive functions, the frontal lobe is the part that is responsible for controlling cognition, emotions, and behavior by consolidating information from all parts of the cerebrum. The functions of the frontal lobe are wide-ranging, but they are all higher-order functions that control and combine higher-order brain functions with some degree of independence, such as speech, behavior, attention, object cognition, and memory.⁷ Therefore, there are many dementia symptoms that originate in impaired frontal lobe functions, and thus an evaluation of frontal lobe functions is important in clinical practice for elderly people. Cognitive flexibility is also referred to as set-shifting and is considered to be an important activity of the frontal lobe.⁸ Cognitive flexibility entails a capacity for varied generation of ideas and perspective shifting. As cognitive flexibility declines, generating ideas and shifting perspectives becomes more difficult, and an individual may become fixated on a single idea or may be unable to perform flexible cognition.⁹ Hence, it can become difficult to adapt to the problems that occur in daily life.

Neuropsychological tests to evaluate cognitive flexibility include the Wisconsin Card Sorting Test (WCST),¹⁰ Trail-Making Test Part B (TMT-B),¹¹ and Verbal Fluency Test (VFT).¹² Although these tests are effective, there are several issues when implementing them among elderly people. WCST is a task that can cause a lot of stress for those taking the test; it takes approximately 30 minutes to complete, and it is not always

Corresponding author: Shinya Takeda, PhD
takedas@tottori-u.ac.jp

Received 2021 January 20

Accepted 2021 March 2

Online published 2021 March 17

Abbreviations: CFT, Cognitive Flexibility Test; FTD, frontotemporal dementia; GDS-15, Geriatric Depression Scale 15; MMSE, Mini Mental State Examination; VFT, Verbal Fluency Test

suitable to elderly people.¹³ In addition, as specific training is needed for the test implementer when implementing WCST, it hasn't been widely adopted in practical medical use. As there is a need for coordination between hand movements and sight in the process of implementing TMT-B, it cannot be implemented if the person has motor or visual impairments, which are common among elderly people. TMT-B has also been found not to have a consistently strong capacity for detecting impairments in frontal lobe functions.¹⁴ One type of VFT uses many words beginning with specific letters, and another type uses many words that belong in specific categories. It has been suggested that low verbal fluency increases the risk of dementia.¹⁵ However, VFT depends on semantic memory that records knowledge¹⁶ and is therefore not a pure assessment of cognitive flexibility.

In light of the above facts, there is a need for a simple test to evaluate the cognitive flexibility of elderly people that does not impose a significant burden on them and can be implemented easily in a short time. Therefore, in this study, a Cognitive Flexibility Test (CFT) was produced that can evaluate cognitive flexibility in a short time and in a simple manner. In this study, the usefulness of CFT was first investigated among healthy elderly people.

SUBJECTS AND METHODS

Participants

In this study, 100 elderly people living at home were asked to cooperate, and 94 of them who consented were included in the study. The selection criterion was that the participants had to be aged 60 years or above. Potential participants were excluded if they had dementia, a visual disability, a hearing disability, aphasia, a neurological disease, or scored 23 points or less on the Mini Mental State Examination (MMSE).¹⁷

Procedure

Two versions of the CFT were produced ("A" and "B"). CFT is a test where the subject is asked to think about alternative uses of an object if it were to be employed for a purpose other than its original intended use. Cognitive flexibility may be explained as the cognitive function of switching from a concept that has already been established in the mind to something different. Based on the assumption that it will be easier to reflect the cognitive flexibility of the subject if they are being tested on objects that are frequently used in daily life, PET bottles and ball-point pens were selected as the items to be tested. Version "A" asked participants the following question: "Other than being used for drinking, what uses does a plastic bottle have? Please list as many

as possible." If the participant could not answer after waiting for 10 seconds, a hint was given, stating, "For example, you could say, 'Use it as a musical instrument by inserting adzuki beans.'" The B version asked participants, "Other than being used for writing, what uses does a ballpoint pen have? Please list as many as possible." If the participant could not answer after waiting for 10 seconds, a hint was given, stating, "For example, you could say, 'It could be used as a bookmark.'" For both the versions of the text, the time limit was two minutes, and the score was the number of uses listed within two minutes. In the case where the subjects' responses were the same as those already mentioned, they were not counted as correct answers. In addition, the responses to the test were dependent on the subject's imagination, and therefore, the validity of these responses were not being evaluated in the test conducted. The test was terminated if no answer was given within 20 seconds of giving a hint to the participant or no other answer was given within 20 seconds of the participant having given an answer.

Evaluation items

Basic information (gender, age, and years of education), CFT, MMSE, VFT, and Geriatric Depression Scale 15 (GDS-15) data were gathered from all the participants. Neuropsychological tests were conducted by certificated psychologists. For VFT, participants listed as many nouns as possible that begin with the sound "ka." First, the basic information and GDS-15 data were collected, and then the MMSE, VFT, CFT-A, and CFT-B tests were conducted in this order.

Statistical analysis

The mean values of the number of responses to the CFT were calculated by age range. If there is a connection between CFT and the number of years of education, it becomes difficult to make sense of CFT. Therefore, the Pearson's correlation coefficient was calculated in order to verify whether there was a relation between CFT and number of years of education. Where a significant relationship was observed, a partial correlation analysis was conducted with the number of years of education as the control variable and the correlation coefficients with other variables were calculated. To investigate the criterion-related validity, the correlation coefficient was calculated with VFT, MMSE, and GDS-15 as the external criteria. In addition, a paired t-test was conducted to investigate the difference in the mean values for CFT and VFT. A paired t-test was also conducted to investigate the difference in the mean values for CFT-A and CFT-B.

Table 1. The mean value and standard deviation for each index by age range

| | Sixties (<i>n</i> = 18) | Seventies (<i>n</i> = 38) | Eighties (<i>n</i> = 32) | Nineties (<i>n</i> = 3) |
|-------------------|--------------------------|----------------------------|---------------------------|--------------------------|
| CFT-A | 6.61 ± 2.09 | 4.45 ± 1.69 | 3.66 ± 1.75 | 1.67 ± 0.58 |
| CFT-B | 3.89 ± 1.94 | 2.00 ± 1.47 | 0.88 ± 1.39 | 0.00 |
| VFT | 10.00 ± 3.09 | 8.21 ± 3.21 | 7.16 ± 2.16 | 4.67 ± 2.08 |
| MMSE | 29.11 ± 1.18 | 28.03 ± 1.64 | 27.69 ± 1.53 | 25.00 ± 4.58 |
| GDS-15 | 3.61 ± 3.33 | 4.42 ± 3.45 | 5.22 ± 3.35 | 3.33 ± 1.15 |
| Age (y.o.) | 66.00 ± 2.95 | 75.40 ± 2.89 | 83.66 ± 2.51 | 91.67 ± 1.53 |
| Education (years) | 13.28 ± 1.90 | 12.32 ± 1.40 | 11.47 ± 1.80 | 5.33 ± 1.15 |

CFT-A, Cognitive Flexibility Test Part A; CFT-B, Cognitive Flexibility Test Part B; GDS-15, Geriatric Depression Scale 15; MMSE, Mini Mental State Examination; VFT, Verbal Fluency Test; y.o., years old.

Table 2. Correlation with each variable corrected for education

| | CFT-A | CFT-B | VFT | MMSE | GDS-15 | Age |
|-------|-------|--------|--------|-------|--------|---------|
| CFT-A | | 0.60** | 0.32** | 0.26* | -0.09 | -0.44** |
| CFT-B | | | 0.46** | 0.19 | -0.16 | -0.46** |
| VFT | | | | 0.12 | -0.14 | -0.22* |
| MMSE | | | | | -0.15 | -0.26* |

***P* < 0.01; **P* < 0.05. CFT-A, Cognitive Flexibility Test Part A; CFT-B, Cognitive Flexibility Test Part B; GDS-15, Geriatric Depression Scale 15; MMSE, Mini Mental State Examination; VFT, Verbal Fluency Test.

Ethical considerations

Participants received an overview of the study and written explanations that data gathered in this study would be analyzed so that individuals could not be identified, only those who consented would be analyzed, and no disadvantages would arise because of consenting or not consenting to participate in the study. The informed consent of subjects was then obtained. This study was approved by the Institutional Review Board of the Faculty of Medicine, Tottori University (No. 19A152). The study was conducted in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki.

RESULTS

Mean values for CFT in each age range

The analysis targeted 91 people, excluding three people who met the exclusion criteria. Of these, 18 were in their sixties, 39 in their seventies, 32 in their eighties, and 3 in their nineties. Table 1 shows the mean value and standard deviation for each index by age range.

In CFT-A, those in their sixties gave 6.61 ± 2.09 answers, those in their seventies gave 4.45 ± 1.69 answers, those in their eighties gave 3.66 ± 1.75 answers, and those in their nineties gave 1.67 ± 0.58 answers. Meanwhile, in CFT-B, those in their sixties gave 3.89 ± 1.94 answers, those in their seventies gave 2.00 ± 1.47

answers, and those in their eighties gave 0.88 ± 1.34 answers. Those in their nineties gave no answers in CFT-B.

Correlation between CFT and years of education

To investigate the correlation between CFT and years of education, the Pearson product-moment correlation coefficient was calculated. For both CFT-A and CFT-B, a moderate positive correlation was found with years of education (CFT-A: 0.49; CFT-B: 0.47). For VFT and MMSE, a mild positive correlation was found with years of education (VFT: 0.37; MMSE: 0.34).

Correlation between CFT and age, VFT, MMSE and GDS-15

The results show that CFT has a moderately positive correlation with the number of years of education in all of the cases. Therefore, after adjusting for the number of years of education by employing partial correlation analysis, the respective correlation coefficients of CFT, age, VFT, MMSE, and GDS-15 were calculated (Table 2). For CFT-A, a moderate negative correlation was found with age, and a mild positive correlation was found with VFT and MMSE, but there was no correlation with GDS-15. For CFT-B, a moderate positive correlation was found with VFT, a moderate negative

correlation was found with age, but there was no correlation with MMSE and GDS-15.

The difference in mean values between VFT and CFT was evaluated by means of a paired t-test. The results indicated that the mean values of CFT-A [$t(90) = 12.00, P < 0.001$] and CFT-B [$t(90) = 23.20, P < 0.001$] were significantly lower than those of VFT. The difference in mean values between CFT-A and CFT-B was evaluated by means of a paired t-test. The results revealed that the mean values of CFT-A [$t(90) = 15.61, P < 0.001$] were significantly higher than CFT-B.

DISCUSSION

The CFT produced here can be implemented easily in a short time, and therefore is an appropriate neuropsychological test for elderly people who may be more prone to fatigue. The procedure is also very simple, and thus the test implementer can use it without any special training.

Cognitive flexibility is highly dependent on the prefrontal cortex, and it demonstrates a capacity to deal with new situations, which often declines with time beyond the age of 70.¹⁰ In both CFT-A and CFT-B, a moderate negative correlation with age was found. These results are consistent with previous study.¹⁰ In VFT, a mild negative correlation with age was found. In prior research on cognitive flexibility using VFT, the results regarding the effect of aging on cognitive flexibility have not been consistent. In some studies, the total words produced were reported to decrease along with age.¹⁸ However, in other studies, the total words produced were not reported to change according to age.¹⁹ Therefore, future studies should seek to clarify how cognitive flexibility is affected by age.

In both CFT-A and CFT-B, a significant positive correlation was found between both the number of responses and years of education. In addition, although this tendency was mild, it was also recognized in MMSE and VFT, and in all the tests, a mild correlation was found with years of education. Other studies have reported that the results of neuropsychological tests and years of education are connected, and that both MMSE and TMT are affected by years of education.^{20, 21} Short duration of education is also a risk factor in AD,²² and it may have a certain impact on cognitive function. Therefore, in CFT, it is necessary to implement the test with consideration for the years of education of the participant in the same way as with other neuropsychological tests.

In CFT-A, a mild positive correlation with MMSE was found. Therefore, the CFT-A may have validity as a neuropsychological test for assessing cognitive function. In CFT-B, however, there were a certain number

of people provided no answers from among the participants. In addition, there was no significant correlation between CFT-B and MMSE. For these reasons, it may be difficult to assess the cognitive flexibility of the elderly people using the CFT-B. In addition, for the tasks in both CFT conditions, a significant correlation with VFT was found. From among the frontal lobe functions, fluency may reflect cognitive flexibility.¹⁰ Therefore, CFT may be valid as an effective tool to evaluate cognitive flexibility from among the frontal lobe functions. VFT evaluates not only frontal lobe functions related to cognitive flexibility but also the knowledge needed to produce linked words.¹⁴ In other words, VFT is understood to be a neuropsychological test that assesses two cognitive functions: frontal lobe functionality and semantic memory. In contrast, CFT requires intellectual activity by converting concepts that are already present in the mind to other objects. CFT requires answers within two minutes, which is one minute longer than the time limit for VFT, but the mean value of the responses given was significantly lower than VFT. This suggests that unlike VFT, CFT does not require cognitive processes to extract answers with a reliance on memory. Based on the above, as an index for measuring cognitive flexibility, CFT may be more appropriate than fluency tasks.

When comparing the number of responses between CFT-A and CFT-B, CFT-B had fewer responses than CFT-A. Cognitive flexibility is an indication of the cognitive function of switching from a concept that has already been established in the mind to something else. Therefore, it may be deduced that the more the concept is already strongly established in the mind, the more difficult it will be to change it to something different. The elderly are more familiar with ball-point pens than pet bottles in relation to frequent daily use. Therefore, the notion that ball-point pens are instruments for writing was already strongly established. This may be the reason the number of responses was lower in comparison to pet bottles. This suggests that the level of difficulty of the problem in CFT is based on how familiar the object is to the subject.

In both CFT-A and CFT-B, a significant correlation with GDS-15 was not found. Therefore, this study did not find an association between CFT and depression in the elderly. It has been clarified that cognitive flexibility is impaired among adults who suffer from depression.^{23, 24} Similarly, the strength of cognitive flexibility is shown to have a connection to improve the quality of life.²⁵ These findings imply that CFT may be useful as an index for ascertaining the mental health of the young people. Therefore, it will be necessary to conduct further investigations in the future as to whether CFT

is useful as an index for evaluating the mental health of the young people.

Finally, there were several limits to this study. CFT can be used as a neuropsychological test to evaluate cognitive flexibility in countries where plastic bottles and ballpoint pens are used. However, it may be that the uses of plastic bottles and ballpoint pens other than that of the intended usage method that are given by participants will be affected by the culture of the country to which participants belong. Therefore, the data obtained here is the result for the Japanese people, and it does not reflect the situation of elderly people living in other countries. In this study, the cutoff value of MMSE was set at 23 points or less, following Anthony et al.¹⁷ However, it is likely that there are many cases of mild cognitive impairment and mild dementia with MMSE scores higher than 24, and this study may not have completely excluded elderly people with cognitive impairment from the subjects. In this study, the reaction latency from the presentation of a task to the subject's response did not evaluate. Evaluating it may allow to examine cognitive flexibility in more detail. Since the objective of this study is to determine whether CFT is effective as a test for evaluating cognitive flexibility, one of the functions of the frontal lobe, we only evaluated its relationship with VFT. Therefore, it is difficult to claim strongly that CFT reflects the frontal lobe functions and cognitive flexibility adequately. It is recommended that further research be conducted to examine the criterion-related validity of CFT by employing FAB and WCST. CFT also comes with problems of interpretation. For both CFT-A and CFT-B, a moderate negative correlation was found with age. In other words, even if a sixty-year old and an eighty-year old both score 3 points for the CFT, the significance of the score is different for these two individuals. Therefore, when trying to interpret the CFT scores, it is imperative that evaluation be conducted in accordance with the standard value by age. It is recommended that in future research, the number of subjects for each age is increased and a follow-up test conducted so as to demonstrate a more accurate standard value of CFT for each age. Frontal lobe functions and fluency declines in frontotemporal dementia (FTD),²⁶ and CFT may support the detection of FTD. However, in this study, as the examinees were not people with FTD, it is unclear as to whether CFT can support the early diagnosis of FTD. In the future, there is a need to perform a large-scale study to evaluate the usefulness of CFT targeting participants with FTD.

In conclusion, CFT-A may be useful as a neuropsychological test that can be implemented easily in a short time to evaluate the cognitive flexibility of elderly

people. In addition, since CFT-A does not require participants to undergo cognitive processes like those of VFT to extract answers with a reliance on memory, it may be that CFT-A is more appropriate than fluency tasks as an indicator of cognitive flexibility.

Acknowledgments: This research was supported by AMED under Grant Number JP20de0107002.

The authors declare no conflict of interest.

REFERENCES

- Zheng G, Liu F, Li S, Huang M, Tao J, Chen L. Tai Chi and the protection of cognitive ability: systematic review of prospective studies in healthy adults. *Am J Prev Med.* 2015;49:89-97. DOI: 10.1016/j.amepre.2015.01.002, PMID: 26094229
- Fratiglioni L, Paillard-Borg S, Winblad B. An active and socially integrated lifestyle in late life might protect against dementia. *Lancet Neurol.* 2004;3:343-53. DOI: 10.1016/S1474-4422(04)00767-7, PMID: 15157849
- World Health Organization. The global dementia observatory reference guide. Genève: World Health Organization; 2018.
- Cheng ST. Cognitive reserve and the prevention of dementia: the role of physical and cognitive activities. *Curr Psychiatry Rep.* 2016;18:85. DOI: 10.1007/s11920-016-0721-2, PMID: 27481112
- Cummings J, Lai TJ, Hemrungronj S, Mohandas E, Yun Kim S, Nair G, et al. Role of Donepezil in the Management of Neuropsychiatric Symptoms in Alzheimer's Disease and Dementia with Lewy Bodies. *CNS Neurosci Ther.* 2016;22:159-66. DOI: 10.1111/cns.12484, PMID: 26778658
- Snyder PJ, Kahle-Wroblewski K, Brannan S, Miller DS, Schindler RJ, DeSanti S, et al. Assessing cognition and function in Alzheimer's disease clinical trials: do we have the right tools? *Alzheimers Dement.* 2014;10:853-60. DOI: 10.1016/j.jalz.2014.07.158, PMID: 25458309
- Stuss DT, Levine B. Adult clinical neuropsychology: lessons from studies of the frontal lobes. *Annu Rev Psychol.* 2002;53:401-33. DOI: 10.1146/annurev.psych.53.100901.135220, PMID: 11752491
- Miyake A, Friedman NP, Emerson MJ, Witzki AH, Howerter A, Wager TD. The unity and diversity of executive functions and their contributions to complex "Frontal Lobe" tasks: a latent variable analysis. *Cognit Psychol.* 2000;41:49-100. DOI: 10.1006/cogp.1999.0734, PMID: 10945922
- Dajani DR, Uddin LQ. Demystifying cognitive flexibility: implications for clinical and developmental neuroscience. *Trends Neurosci.* 2015;38:571-8. DOI: 10.1016/j.tins.2015.07.003, PMID: 26343956
- Milner B. Effects of different brain lesions on card sorting. *Arch Neurol.* 1963;9:90-100. DOI: 10.1001/archneur.1963.00460070100010
- Butler M, Retzlaff PD, Vanderploeg R. Neuropsychological test usage. *Prof Psychol Res Pr.* 1991;22:510-2. DOI: 10.1037/0735-7028.22.6.510
- Lezak MD, Howieson DB, Bigler ED, Tranel D. *Neuropsychological Assessment*, 5th ed. NY: Oxford University Press; 2012.

- 13 Bryan J, Luszcz MA. Measurement of executive function: considerations for detecting adult age differences. *J Clin Exp Neuropsychol*. 2000;22:40-55. DOI: [10.1076/1380-3395\(200002\)22:1;1-8;FT040](https://doi.org/10.1076/1380-3395(200002)22:1;1-8;FT040), PMID: [10649544](https://pubmed.ncbi.nlm.nih.gov/10649544/)
- 14 Chan E, MacPherson SE, Robinson G, Turner M, Lecce F, Shallice T, et al. Limitations of the trail making test part-B in assessing frontal executive dysfunction. *J Int Neuropsychol Soc*. 2015;21:169-74. DOI: [10.1017/S135561771500003X](https://doi.org/10.1017/S135561771500003X), PMID: [25697352](https://pubmed.ncbi.nlm.nih.gov/25697352/)
- 15 Sutin AR, Stephan Y, Terracciano A. Verbal fluency and risk of dementia. *Int J Geriatr Psychiatry*. 2019;34:863-7. DOI: [10.1002/gps.5081](https://doi.org/10.1002/gps.5081), PMID: [30729575](https://pubmed.ncbi.nlm.nih.gov/30729575/)
- 16 Shao Z, Janse E, Visser K, Meyer AS. What do verbal fluency tasks measure? Predictors of verbal fluency performance in older adults. *Front Psychol*. 2014;5:772. DOI: [10.3389/fpsyg.2014.00772](https://doi.org/10.3389/fpsyg.2014.00772), PMID: [25101034](https://pubmed.ncbi.nlm.nih.gov/25101034/)
- 17 Anthony JC, LeResche L, Niaz U, Von Korff MR, Folstein MF. Limits of the 'Mini-Mental State' as a screening test for dementia and delirium among hospital patients. *Psychol Med*. 1982;12:397-408. DOI: [10.1017/S0033291700046730](https://doi.org/10.1017/S0033291700046730), PMID: [7100362](https://pubmed.ncbi.nlm.nih.gov/7100362/)
- 18 Rodriguez-Aranda C, Martinussen M. Age-related differences in performance of phonemic verbal fluency measured by Controlled Oral Word Association Task (COWAT): a meta-analytic study. *Dev Neuropsychol*. 2006;30:697-717. DOI: [10.1207/s15326942dn3002_3](https://doi.org/10.1207/s15326942dn3002_3), PMID: [16995832](https://pubmed.ncbi.nlm.nih.gov/16995832/)
- 19 Troyer AK, Moscovitch M, Winocur G. Clustering and switching as two components of verbal fluency: evidence from younger and older healthy adults. *Neuropsychology*. 1997;11:138-46. DOI: [10.1037/0894-4105.11.1.138](https://doi.org/10.1037/0894-4105.11.1.138), PMID: [9055277](https://pubmed.ncbi.nlm.nih.gov/9055277/)
- 20 Crum RM, Anthony JC, Bassett SS, Folstein MF. Population-based norms for the Mini-Mental State Examination by age and educational level. *JAMA*. 1993;269:2386-91. DOI: [10.1001/jama.1993.03500180078038](https://doi.org/10.1001/jama.1993.03500180078038), PMID: [8479064](https://pubmed.ncbi.nlm.nih.gov/8479064/)
- 21 Olivera-Souza RD, Moll J, Passman LJ, Cunha FC, Paes F, Adriano MV, et al. Trail making and cognitive set-shifting. *Arq Neuropsiquiatr*. 2000;58:826-9. DOI: [10.1590/S0004-282X2000000500006](https://doi.org/10.1590/S0004-282X2000000500006), PMID: [11018818](https://pubmed.ncbi.nlm.nih.gov/11018818/)
- 22 Vanhanen M, Koivisto K, Moilanen L, Helkala EL, Hänninen T, Soininen H, et al. Association of metabolic syndrome with Alzheimer disease: A population-based study. *Neurology*. 2006;67:843-7. DOI: [10.1212/01.wnl.0000234037.91185.99](https://doi.org/10.1212/01.wnl.0000234037.91185.99), PMID: [16966548](https://pubmed.ncbi.nlm.nih.gov/16966548/)
- 23 Deveney CM, Deldin PJ. A preliminary investigation of cognitive flexibility for emotional information in major depressive disorder and non-psychiatric controls. *Emotion*. 2006;6:429-37. DOI: [10.1037/1528-3542.6.3.429](https://doi.org/10.1037/1528-3542.6.3.429), PMID: [16938084](https://pubmed.ncbi.nlm.nih.gov/16938084/)
- 24 McClintock SM, Husain MM, Greer TL, Cullum CM. Association between depression severity and neurocognitive function in major depressive disorder: A review and synthesis. *Neuropsychology*. 2010;24:9-34. DOI: [10.1037/a0017336](https://doi.org/10.1037/a0017336), PMID: [20063944](https://pubmed.ncbi.nlm.nih.gov/20063944/)
- 25 Davis JC, Marra CA, Najafzadeh M, Liu-Ambrose T. The independent contribution of executive functions to health related quality of life in older women. *BMC Geriatr*. 2010;10:16. DOI: [10.1186/1471-2318-10-16](https://doi.org/10.1186/1471-2318-10-16), PMID: [20359355](https://pubmed.ncbi.nlm.nih.gov/20359355/)
- 26 Libon DJ, McMillan C, Gunawardena D, Powers C, Massimo L, Khan A, et al. Neurocognitive contributions to verbal fluency deficits in frontotemporal lobar degeneration. *Neurology*. 2009;73:535-42. DOI: [10.1212/WNL.0b013e3181b2a4f5](https://doi.org/10.1212/WNL.0b013e3181b2a4f5), PMID: [19687454](https://pubmed.ncbi.nlm.nih.gov/19687454/)