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Association Between a Functional Polymorphism of the BDNF Gene and Visuospatial Memory in a Sample of Neurofibromatosis Type 1

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Objective: Neurofibromatosis type 1 (NF1) is a common single genetic disorder. A rarely investigated source of phenotypic variance in NF1 is the genetic modifiers. In this study, we tested whether the Val66Met Brain-Derived Neurotrophic Factor polymorphism (*BDNF*) was associated with three memory aspects in a small NF1 sample: Working Memory, Visuospatial Memory, and Auditory-Verbal Memory. ***Method:*** Thirty-four NF1 participants performed the Digit-Span Task, the Corsi Block-Tapping Task, the Rey Auditory-Verbal Learning Test, and the Rey–Osterrieth complex figure from which the distinct memory aspects were extracted through factorial analysis. ***Results:*** We found a specific pattern of association between the Val66Met *BDNF* polymorphism and visuospatial memory in NF1 individuals. Met carriers showed worse performance in visuospatial memory, but not verbal or working memory. ***Conclusion:*** The hypothesis of genetic modifiers as a potential source of variability in the NF1 phenotype seems plausible and is supported by growing evidence regarding several domains, including cognition.

Public Significance Statement
NF1 is a rare genetic disorder associated with cognitive deficits. In this study, we investigate impairments in memory. The *BDNF* alleles might modulate the memory of an individual with NF1. Memory content related to visual and spatial information is associated with the *BDNF* gene in patients with NF1.

Keywords: neurofibromatosis, memory, brain-derived neurotrophic factor, learning, spatial learning

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Neurofibromatosis type 1 (NF1) is a common single-gene disorder (incidence ~ 1/3,000) associated with cognitive impairments, learning disabilities, and behavioral problems (Friedman, 1999; North, 2000; Pasmant et al., 2012; Shilyansky et al., 2010). Despite a known molecular basis, the NF1 phenotype is markedly heterogeneous and unpredictable, a feature hardly explained by the *NF1* gene alone (Pasmant et al., 2012; Shilyansky et al., 2010). Cognitive impairment in NF1 is a major concern for patients and clinicians, likely associated with academic underachievement and

behavioral symptoms with lifetime consequences (North, 2000). Up to 80% of NF1 patients will present mild to severe cognitive problems in at least one cognitive function (Hachon et al., 2011; Lehtonen et al., 2013). However, failure in predicting individual differences among NF1 patients may represent one of the major barriers in designing successful therapeutic strategies (Schwetye & Gutmann, 2014).

Brain structural alterations were the main investigated feature in the search for the pathophysiology of the NF1 cognitive impairments in humans (Duarte et al., 2014). As a group, NF1 individuals show increased total brain volume and specific abnormalities in structures such as the corpus callosum. Compared with typically developing individuals, subtle differences were also found in the hippocampus, basal ganglia, thalamus, and visual cortex, especially regarding gray matter relative volume (Duarte et al., 2014), although there is heterogeneity in these results (Duarte et al., 2014).

Endogenous factors play a crucial role in individual differences in human development (Belsky & Pluess, 2009). For NF1, genetic modifiers were pointed out as a potential influence explaining such a variable phenotype in this monogenetic disorder (Carey & Viskochil, 1999; Pasmant et al., 2012; Shilyansky et al., 2010). Genetic modifiers unlinked to the *NF1*gene loc greatly contribute to NF1 phenotypic variation in the number of cutaneous neurofibromas and café-au-lait macules, for example (e.g., Bahuau et al., 2001; Titze et al., 2010; Mußotter et al., 2012; Pemov et al., 2014). The hypothesis of common genetic variations influencing individual differences in NF1 also extends to cognition, but only one study was conducted in this population so far. Recently, our group found an association between the *COMT* gene *(rs4680)* and verbal working memory in an NF1 sample (Costa et al., 2014). Human cognition is a complex trait influenced by common genetic variants with many genes pruning to small effect sizes (Manolio et al., 2009). Along with the *COMT* gene, the *BDNF* gene has been widely studied and might be one of the most promising genes involved in the molecular genetics of cognition (Savitz et al., 2006).

The *BDNF* gene is located at 11p14.1 and encodes the brain-derived neurotrophic factor (BDNF), which regulates synaptic plasticity and brain connectivity due to its role in proliferation, differentiation, and the fate of neuronal cells (Houlihan et al., 2009). Despite its potential influence across several functions, the *BDNF* influences hippocampal functioning and memory (Lau et al., 2010, ref). Studies with the Val66Met variant of the *BDNF* gene *(rs6265)* suggested that individuals carrying the Met allele (with one or more copies) show decreased cognitive performance (Dincheva et al., 2012; Kambeitz et al., 2012). The expression of the Met allele results in a lower activity-dependent secretion of BDNF and abnormalities in the intracellular BDNF trafficking (Egan et al., 2003). In this study, we tested whether the Val66Met *BDNF* polymorphism was associated with memory performance in NF1 patients. Memory is composed of multiple systems, and all of them are required for everyday problem-solving functional adaptation, and adequate performance in activities of daily living (de Paula et al., 2015; Gold, 2012; Squire, 2004).

In the NF1 population, deficits in working memory are common and usually severe, while impairments in long-term memory systems such as memory are less frequent and heterogeneous (Bawden et al., 1996; Hachon et al., 2011; Hyman et al., 2005; Krab et al., 2008). In turn, the influence of the Val66Met *BDNF* polymorphism on long-term memory is less controversial in the literature compared to the *BDNF* influence on working memory (Chen et al., 2015; Montag et al., 2014). Therefore, we expected to observe higher differences between the genotype groups in memory compared to working memory.

Method

Participants

As stated before, NF1 prevalence is about 1 in 3000, which reduces the access to this clinical population, limiting the sample sizes for most of the studies. In a specialized clinic in Neurofibromatosis a convenience sample of 33 NF1 patients was enrolled in this study. They were invited to participate in broader research approved by the local ethics committee about the molecular mechanisms of this disease. All participants and their parents (in the case of children and adolescents) gave written consent for participation.

Participants had a mean age of 22.0 ± 11.4 years (ranging 6–50 years) and a mean formal education of 7.9 ± 3.6 (ranging 1–15 years. IQ average, measured by the Wechsler Intelligence Scale III

(WISC-III or WAIS-III), was 93.7 ± 14.0 (ranging 63–121). There were more males ($N = 18$, 54%) than female ($N = 15$, 46%) participants.

Memory Assessment and Neuropsychological Data Modeling

For the assessment of working memory, we used the Digit-Span Task and the Corsi Block-Tapping Task (Kessels et al., 2008). These are simple span tasks in which the participant must repeat a series of numbers (Digit Span) or movements in a wooden board (Corsi Block-Tapping Task) of increasing difficulty. We measured both the forward span (which is more related to the phonological loop/visuospatial sketchpad working memory) and the backward span (which is linked to the central executive system of working memory). We used the total of correct trials as a measure of working memory performance on each task. Higher scores are representative of better performance.

The assessment of memory retrieval was performed using the Brazilian version of the Rey Auditory-Verbal Learning Test (RAVLT; Malloy-Diniz et al., 2007) and the Rey–Osterrieth complex figure test (ROCF; Rey, 1941; Shin et al., 2006). These are traditional measures of memory and evaluate both verbal (RAVLT) and visuospatial (ROCF) aspects of memory retrieval. To better match the two tasks, we used the immediate and delayed recall trials from both tasks. Scores in the RAVLT range from 0 to 15 in each recall trial and 0 to 36 in the ROCF.

Impairment in each neuropsychological test was defined when performance was below percentile five according to normative data. We adopted a principal component analysis for neuropsychological data modeling. All the eight neuropsychological measures (Digit Span Forward, Digit Span Backward, Corsi Span Forward, Corsi Span Backward, RAVLT Immediate Recall, RAVLT Delayed Recall, ROCF Immediate Recall, and ROCF Delayed Recall) underwent the procedure, in which we adopted an oblique rotation method (direct oblimin) to reduce the number of measures. Component extraction criteria were Eigenvalues larger than 1 and scree plot analysis.

The procedure generated three components, which accounted for 75% of the model variance. One variable showed factor loads above 0.4 in two components (Corsi Span Forward), so we allocated this variable where it shows the higher factor load. Component one answered for 36% of the model variance and was formed by RAVLT delayed recall (factor load 0.963), RAVLT immediate recall (factor load 0.960), and digit span backward (factor load 0.461), thus named *verbal memory*. Component two answered for 25% of the model variance and was formed Rey Complex Figure immediate recall (factor load −0.936), Rey Complex Figure delayed recall (factor load −0.928) and by Corsi Span Forward (factor load −0.521) thus named *visuospatial memory*. Component three answered for 15% of model variance contained the *working memory* measures, Digit Span Backward (factor load 0.937), and Corsi Span Backward (factor load 0.673). The components were extracted by the Anderson-Rubin method of SPSS 20.0 and used in the following procedures.

BDNF Genotyping

Genomic DNA was extracted from blood samples using the high salt method (Lahiri & Nurnberger, 1991). The *BDNF* functional polymorphism (val66met, rs6265) was purchased in a made-to-order from Applied Biosystems®. Genotyping was performed using a real-time PCR system in the allelic discrimination mode (Stratagene Mx3005—MxPro QPCR Software, 2007) using the TaqMan Genotyping Master Mix (Applied Biosystems, Foster City, CA). PCR parameters included an initial denaturation at 95 °C for 10 min, followed by 50 cycles at 95 °C for 15 s and 60 °C for 1 min. Each reaction contained 3.5 μl of Mix, 0.1 μl of the probe, 3.4 μl of deionized water, and 1.0 μl of DNA. These procedures were detailed in a previous study (Figueira et al., 2010). Researchers involved in genotyping were blind to the neuropsychological results, and researchers participating in the neuropsychological assessments were blind to the genotyping results. *BDNF* genotype was coded as a categorical variable: Val/Val ($n = 20$), and Val/Met+Met/Met ($n = 13$) for further analysis.

Statistical Procedures

Neuropsychological data (IQ, Working Memory, Visuospatial Memory, and Auditory-Verbal Memory) and age were normally distributed according to Shapiro–Wilk tests and histogram analysis. Comparisons between the groups regarding

Table 1
Participants' Description of Demographic and Cognitive Measures

	Val/Val (n = 20)		Val/Met + Met/Met (n = 13)		—
Measure	Mean	*SD*	Mean	*SD*	% Impaired[a]
Age	21.45	12.42	22.38	10.41	—
Education	7.65	3.92	8.08	2.96	—
IQ	93.30	12.91	93.54	16.24	11%
Digit span forward	6.40	1.90	6.38	1.66	0%
Digit span backward	3.60	1.43	4.00	1.63	3%
Corsi span forward	6.60	2.41	6.08	2.29	32%
Corsi span backward	4.15	2.37	3.92	1.89	56%
ROCF (IR)	16.18	6.96	11.46	6.85	38%
ROCF (DR)	15.78	7.56	11.92	6.13	35%
RAVLT (IR)	6.60	2.41	6.08	2.29	18%
RAVLT (DR)	4.15	2.37	3.92	1.89	26%

BDNF: Brain-Derived Neurotrophic Factor, IR: Immediate Recall, ROCF: Rey–Osterrieth Complex Figure test, RAVLT: Rey Auditory-Verbal Learning Test, IQ: Intelligence Quotient. *N*: sample size, *M:* mean, *SD*: standard deviation, Min: minimum, Max: maximum.
[a] 1.5 *SD* below the expected age-corrected normative data.

sociodemographic measures were performed by chi-square tests or independent samples *t*-tests. We adopted a multivariate analysis of variance to test the association between *BDNF* and memory. The three memory variables were entered as dependent variables, *BDNF* and sex as fixed factors, and age, formal education, and IQ as covariates. These procedures were performed in SPSS 22.0.

Results

Participants' description is shown in Table 1. Sociodemographic characteristics and overall cognitive performance were very heterogeneous in our sample, a pattern usually observed in NF1. We found no significant differences between Val/Val and Val/Met+Met/Met participants regarding sex (50% female, 46% female, $\chi^2 = 0.01$ $p = .394$), Age ($21.45 \pm 12.42 \times 22.38 \pm 10.41$, $t = -0.15$, $p = .880$), Education ($7.65 \pm 3.92 \times 8.08 \pm 2.96$, $t = -0.17$, $p = .864$) or IQ ($93.30 \pm 12.91 \times 93.54 \pm 16.24$, $t = 0.06$, $p = .950$).

Table 2 shows the results of a multivariate analysis of variance. For working memory, we found significant main effects of IQ ($p < .001, \eta_p^2 = 0.43$) and formal education ($p = .024, \eta_p^2 = 0.16$), but no significant effects of age ($p = .940$), sex ($p = .883$) or *BDNF* ($p = .163$). For the auditory-verbal memory, we found the main effect of IQ ($p = .050$, $\eta_p^2 = 0.13$), but not Education ($p = .156$), BDNF genotype (0.888), age ($p = .940$) and sex ($p = .506$) were not significant. The visuospatial memory showed a different pattern of association with main effects for education ($p = .018$, $\eta_p^2 = 0.18$) and a significant effect of the *BDNF* genotype on memory performance ($p = .028$, $\eta_p^2 = 0.16$), albeit no significant effect of age ($p = .878$), sex ($p = .505$) or IQ ($p = .642$).

The effect of the *BDNF* genotype on the visuospatial memory can be considered large according to

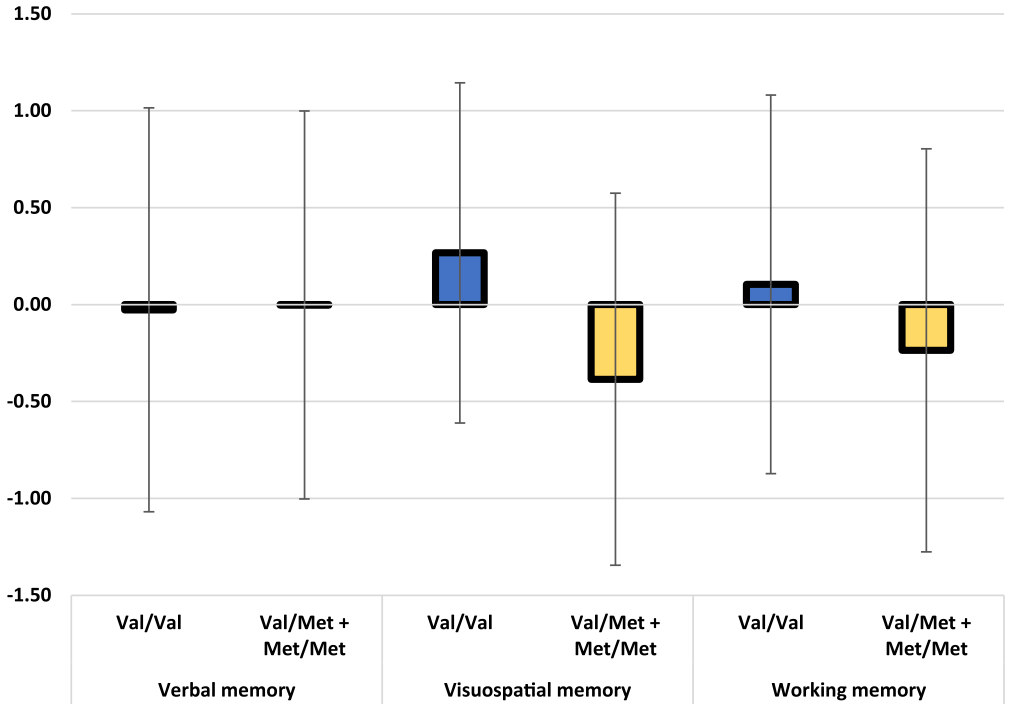
Table 2
Main Effects of Age, IQ, Education and BDNF *Genotype on Different Aspects of Memory, Assessed by a Multivariate Analysis of Variance Model*

Component	Factor/covariate	p	η_p^2
Working Memory	IQ	<.001	0.43
	Education	.024	0.16
	BDNF group	.163	—
	Age	.940	—
	Sex	.883	—
Verbal	IQ	.050	0.13
	Education	.156	—
	BDNF group	.888	—
	Age	.940	—
	Sex	.506	
Visuospatial	IQ	.642	—
	Education	.018	0.18
	BDNF group	.028	0.16
	Age	.878	—
	Sex	.505	—

BDNF: Brain-Derived Neurotrophic Factor.

Figure 1

Estimated Marginal Means Controlled by Sociodemographic Factors and IQ for Each Memory Component (Z-Score) According to BDNF *Genotypes. Higher Scores Indicated Better Performance*



most statistic guidelines. A post hoc comparison (Figure 1) between the estimated marginal means (EMM) in the visuospatial memory component between the Val/Val (EMM = 0.27, *SE* = 0.19) and Val/Met+Met/Met (EMM = −0.43, *SE* = 0.24) groups was significant ($p = .032$).

Discussion

This study investigated the association between the Val66Met *BDNF* polymorphism and performance in three memory components extracted from a factorial analysis (verbal, visuospatial, and working memory) in a small sample of NF1 individuals. The *BDNF* gene main effect was observed only on the Visuospatial Memory component, which was formed by the immediate and delayed recalls of the Rey–Osterrieth complex figure test and the Corsi Block-Tapping test (forward). Met carriers showed reduced performance in this function. The *BDNF* gene effect on visuospatial memory was significant after controlling for sociodemographic and IQ data.

The Val66Met *BDNF* polymorphism has been more consistently associated with performance in memory tests, but its relation to working memory seems controversial (Chen et al., 2015; Egan et al., 2003). On the other hand, recently we found an effect of the Val158Met *COMT* polymorphism, a gene influencing dopamine-mediated functions, on the NF1 capacity of mental manipulation of information in working memory (Costa et al., 2014). These results suggest a potentially major role of the BDNF on long-term memory systems rather than on short-term memory systems.

Noteworthy, only the visuospatial memory was influenced by the *BDNF* genotype in this study. The Rey–Osterrieth complex figure test differs from the Rey Auditory-Verbal Learning Test in content (visuospatial vs. verbal) and structure (recall vs. learning and recall). In the Rey complex figure, the subject has only one trial for stimuli memorization (copy trial), a structure different from the RAVLT,

where the subject is exposed to information in five learning trials. Clinical data suggest that, although difficult in the early stages of learning is common in NF1 patients, they can benefit from multiples presentations, repetitions, focused training, and application of other cognitive resources in the learning process (Hyman et al., 2005).

Additionally, deficits in visuospatial processing are the most common and consistent finding in NF1 (Lehtonen et al., 2013), which may heighten individual differences in the recollection of material requiring visuospatial interpretation (Lewin et al., 2001). Impairment in visuospatial memory was previously reported in NF1 (van der Vaart et al., 2016).

BDNF is recognized as an important molecule for the induction of long-term potentiation (LTP) in the hippocampus, one of the major cellular mechanisms underlying memory formation and persistence (Bekinschtein et al., 2007; Bliss & Collingridge, 1993). Studies using animal models of NF1 have shown an association between impaired spatial learning (hippocampal-based learning) and abnormalities in LTP which seems to occur in both early-phase (immediate learning) and long-term (long-term memory formation) LTP maintenance (Costa et al., 2002; Guilding et al., 2007; Ho et al., 2007; Silva et al., 1997). Moreover, Duarte et al. (2014) suggest that structural hippocampal abnormality in NF1 patients' may be associated with difficulties in visual and spatial learning and memory function. Future studies are needed to investigate whether a higher visuospatial memory inefficiency in NF1 *BDNF* Met carriers is due to an additive hippocampal pathology (Bueller et al., 2006; Egan et al., 2003, Molendijk et al., 2012).

As a secondary result, we found a significant effect of formal education in the performance of the Rey–Osterrieth complex figure immediate and delayed recall. This is a conflicting result according to several studies, as reviewed by Strauss et al. (2006). If participants have at least secondary level education the effect seems negligible or fully accounted for by IQ (Boone et al., 1993). However, in people with low formal education this effect is significant and a major confounding for test interpretation, as in most drawing tasks, due to unfamiliarity with the pen-paper/drawing interface (de Paula et al., 2013; Rosselli & Ardila, 2003). Since our sample has a relatively low formal education we believe this may have contributed to the significant association.

The number of participants included in this study is one of its main limitations. We were only able to detect large differences between the groups. Studies using a candidate gene approach are often limited by sample power since complex traits are likely to be influenced by a plethora of genes with small effects (Mandelman & Grigorenko, 2012; Manolio et al., 2009). The candidate gene approach may be particularly daunting in the study of complex phenotypes of rare conditions such as NF1. However, it is at least intriguing the fact that we found a large difference in visuospatial memory depending on the *BDNF* genotype in this small sample of NF1 participants. *NF1* gene alteration brings this cascade of brain abnormalities that might change the strength of normal genetic variations, exacerbating its effects. Future studies comparing the effects of single-nucleotide polymorphisms on complex traits in different populations as opposed to the NF1 population have the potential to investigate a moderator role of the *NF1* gene on normal genetic variation influencing cognition. Additionally, some of the possible sources of variation in *BDNF* studies such as age and education (Hashimoto et al., 2016) were only statistically controlled in the present study.

Conclusion

We found a specific pattern of association between the Val66Met *BDNF* polymorphism and visuospatial memory in NF1 individuals. Met carriers showed worse performance in visuospatial memory but not in auditory-verbal memory or working memory. The hypothesis of genetic modifiers as potential influences of the NF1 variable phenotype seems plausible with evidence growing regarding several features such as cognition.

References

Bahuau, M., Pelet, A., Vidaud, D., Lamireau, T., LeBail, B., Munnich, A., Vidaud, M., Lyonnet, S., & Lacombe, D. (2001). GDNF as a candidate modifier in a type 1 neurofibromatosis (NF1) enteric phenotype. *Journal of Medical Genetics*, *38*(9), 638–643. https://doi.org/10.1136/jmg.38.9.638

Bawden, H., Dooley, J., Buckley, D., Camfield, P., Gordon, K., Riding, M., & Llewellyn, G. (1996). MRI and nonverbal cognitive deficits in children with neurofibromatosis 1. *Journal of Clinical and Experimental Neuropsychology*, *18*(6), 784–792. https://doi.org/10.1080/01688639608408302

Bekinschtein, P., Cammarota, M., Igaz, L. M., Bevilaqua, L. R., Izquierdo, I., & Medina, J. H. (2007). Persistence of long-term memory storage

requires a late protein synthesis- and BDNF-dependent phase in the hippocampus. *Neuron*, *53*(2), 261–277. https://doi.org/10.1016/j.neuron.2006.11.025

Belsky, J., & Pluess, M. (2009). Beyond diathesis stress: Differential susceptibility to environmental influences. *Psychological Bulletin*, *135*(6), 885–908. https://doi.org/10.1037/a0017376

Bliss, T. V., & Collingridge, G. L. (1993). A synaptic model of memory: Long-term potentiation in the hippocampus. *Nature*, *361*(6407), 31–39. https://doi.org/10.1038/361031a0

Boone, K. B., Lesser, I. M., Hill-Gutierrez, E., Berman, N. G., & D'Elia, L. F. (1993). Rey-Osterrieth Complex Figure performance in healthy, older adults: Relationship to age, education, sex, and IQ. *Clinical Neuropsychologist*, *7*, 22–28. https://doi.org/10.1080/13854049308401884

Bueller, J. A., Aftab, M., Sen, S., Gomez-Hassan, D., Burmeister, M., & Zubieta, J. K. (2006). *BDNF* Val66Met allele is associated with reduced hippocampal volume in healthy subjects. *Biological Psychiatry*, *59*(9), 812–815. https://doi.org/10.1016/j.biopsych.2005.09.022

Carey, J. C., & Viskochil, D. H. (1999). Neurofibromatosis type 1: A model condition for the study of the molecular basis of variable expressivity in human disorders. *American Journal of Medical Genetics*, *89*(1), 7–13.

Chen, C.-C., Chen, C.-J., Wu, D., Chi, N.-F., Chen, P.-C., Liao, Y.-P., Chiu, H.-W., & Hu, C.-J. (2015). *BDNF* Val66Met polymorphism on functional MRI during n-back working memory tasks. *Medicine*, *94*(42), Article e1586. https://doi.org/10.1097/MD.0000000000001586

Costa, D. S., de Paula, J. J., de Rezende, N. A., Rodrigues, L. O. C., Malloy-Diniz, L. F., Romano-Silva, M. A., & Miranda, D. M. (2014). Neuropsychological impairments in elderly Neurofibromatosis type 1 patients. *European Journal of Medical Genetics*, *57*(5), 216–219. https://doi.org/10.1016/j.ejmg.2014.02.004

Costa, R. M., Federov, N. B., Kogan, J. H., Murphy, G. G., Stern, J., Ohno, M., Kucherlapati, R., Jacks, T., & Silva, A. J. (2002). Mechanism for the learning deficits in a mouse model of neurofibromatosis type 1. *Nature*, *415*(6871), 526–530. https://doi.org/10.1038/nature711

de Paula, J. J., Costa, M. V., Bocardi, M. B., Cortezzi, M., De Moraes, E. N., & Malloy-Diniz, L. F. (2013). The Stick Design Test on the assessment of older adults with low formal education: Evidences of construct, criterion-related and ecological validity. *International Psychogeriatrics*, *25*(12), 2057–2065. https://doi.org/10.1017/S1041610213001282

de Paula, J. J., Diniz, B. S., Bicalho, M. A., Albuquerque, M. R., Nicolato, R., de Moraes, E. N., Romano-Silva, M. A., & Malloy-Diniz, L. F. (2015). Specific cognitive functions and depressive symptoms as predictors of activities of daily living in older adults with heterogeneous cognitive backgrounds. *Frontiers in Aging Neuroscience*, *7*, Article 139. https://doi.org/10.3389/fnagi.2015.00139

Dincheva, I., Glatt, C. E., & Lee, F. S. (2012). Impact of the *BDNF* Val66Met polymorphism on cognition: Implications for behavioral genetics. *The Neuroscientist*, *18*(5), 439–451. https://doi.org/10.1177/1073858411431646

Duarte, J. V., Ribeiro, M. J., Violante, I. R., Cunha, G., Silva, E., & Castelo-Branco, M. (2014). Multivariate pattern analysis reveals subtle brain anomalies relevant to the cognitive phenotype in neurofibromatosis type 1. *Human Brain Mapping*, *35*(1), 89–106. https://doi.org/10.1002/hbm.22161

Egan, M. F., Kojima, M., Callicott, J. H., Goldberg, T. E., Kolachana, B. S., Bertolino, A., Zaitsev, E., Gold, B., Goldman, D., Dean, M., Lu, B., & Weinberger, D. R. (2003). The *BDNF* val66met polymorphism affects activity-dependent secretion of BDNF and human memory and hippocampal function. *Cell*, *112*(2), 257–269. https://doi.org/10.1016/S0092-8674(03)00035-7

Figueira, P., Malloy-Diniz, L., Campos, S. B., Miranda, D. M., Romano-Silva, M. A., De Marco, L., Neves, F. S., & Correa, H. (2010). An association study between the Val66Met polymorphism of the *BDNF* gene and postpartum depression. *Archives of Women's Mental Health*, *13*(3), 285–289. https://doi.org/10.1007/s00737-010-0146-6

Friedman, J. M. (1999). Epidemiology of neurofibromatosis type 1. *American Journal of Medical Genetics*, *89*(1), 1–6. https://doi.org/10.1002/(SICI)1096-8628(19990326)89:1<1:AID-AJMG3>3.0.CO;2-8

Gold, D. A. (2012). An examination of instrumental activities of daily living assessment in older adults and mild cognitive impairment. *Journal of Clinical and Experimental Neuropsychology*, *34*(1), 11–34. https://doi.org/10.1080/13803395.2011.614598

Guilding, C., McNair, K., Stone, T. W., & Morris, B. J. (2007). Restored plasticity in a mouse model of neurofibromatosis type 1 via inhibition of hyperactive ERK and CREB. *The European Journal of Neuroscience*, *25*(1), 99–105. https://doi.org/10.1111/j.1460-9568.2006.05238.x

Hachon, C., Iannuzzi, S., & Chaix, Y. (2011). Behavioural and cognitive phenotypes in children with neurofibromatosis type 1 (NF1): The link with the neurobiological level. *Brain & Development*, *33*(1), 52–61. https://doi.org/10.1016/j.braindev.2009.12.008

Hashimoto, T., Fukui, K., Takeuchi, H., Yokota, S., Kikuchi, Y., Tomita, H., Taki, Y., & Kawashima, R. (2016). Effects of the *BDNF* Val66Met polymorphism on gray matter volume in typically developing children and adolescents. *Cerebral Cortex*, *26*(4), 1795–1803. https://doi.org/10.1093/cercor/bhw020

Ho, I. S., Hannan, F., Guo, H. F., Hakker, I., & Zhong, Y. (2007). Distinct functional domains of neurofibromatosis type 1 regulate immediate versus long-term memory formation. *The Journal of Neuroscience*, *27*(25), 6852–6857. https://doi.org/10.1523/JNEUROSCI.0933-07.2007

Houlihan, L. M., Harris, S. E., Luciano, M., Gow, A. J., Starr, J. M., Visscher, P. M., & Deary, I. J. (2009). Replication study of candidate genes for cognitive abilities: The Lothian Birth Cohort 1936. *Genes Brain & Behavior*, *8*(2), 238–247. https://doi.org/10.1111/j.1601-183X.2008.00470.x

Hyman, S. L., Shores, A., & North, K. N. (2005). The nature and frequency of cognitive deficits in children with neurofibromatosis type 1. *Neurology*, *65*(7), 1037–1044. https://doi.org/10.1212/01.wnl.0000179303.72345.ce

Kambeitz, J. P., Bhattacharyya, S., Kambeitz-Ilankovic, L. M., Valli, I., Collier, D. A., & McGuire, P. (2012). Effect of *BDNF* val(66)met polymorphism on declarative memory and its neural substrate: A meta-analysis. *Neuroscience and Biobehavioral Reviews*, *36*(9), 2165–2177. https://doi.org/10.1016/j.neubiorev.2012.07.002

Kessels, R. P., van den Berg, E., Ruis, C., & Brands, A. M. (2008). The backward span of the Corsi Block-Tapping Task and its association with the WAIS-III Digit Span. *Assessment*, *15*(4), 426–434. https://doi.org/10.1177/1073191108315611

Krab, L. C., Aarsen, F. K., de Goede-Bolder, A., Catsman-Berrevoets, C. E., Arts, W. F., Moll, H. A., & Elgersma, Y. (2008). Impact of neurofibromatosis type 1 on school performance. *Journal of Child Neurology*, *23*(9), 1002–1010. https://doi.org/10.1177/0883073808316366

Lahiri, D. K., & Nurnberger, J. I., Jr. (1991). A rapid non-enzymatic method for the preparation of HMW DNA from blood for RFLP studies. *Nucleic Acids Research*, *19*(19), Article 5444. https://doi.org/10.1093/nar/19.19.5444

Lau, A. G., Irier, H. A., Gu, J., Tian, D., Ku, L., Liu, G., Xia, M., Fritsch, B., Zheng, J. Q., Dingledine, R., Xu, B., Lu, B., & Feng, Y. (2010). Distinct 3'UTRs differentially regulate activity-dependent translation of brain-derived neurotrophic factor (BDNF). *Proceedings of the National Academy of Sciences of the United States of America*, *107*(36), 15945–15950. https://doi.org/10.1073/pnas.1002929107

Lehtonen, A., Howie, E., Trump, D., & Huson, S. M. (2013). Behaviour in children with neurofibromatosis type 1: Cognition, executive function, attention, emotion, and social competence. *Developmental Medicine and Child Neurology*, *55*(2), 111–125. https://doi.org/10.1111/j.1469-8749.2012.04399.x

Lewin, C., Wolgers, G., & Herlitz, A. (2001). Sex differences favoring women in verbal but not in visuospatial episodic memory. *Neuropsychology*, *15*(2), 165–173. https://doi.org/10.1037/0894-4105.15.2.165

Malloy-Diniz, L. F., Lasmar, V. A. P., Gazinelli, L. S., Fuentes, D., & Salgado, J. V. (2007). The Rey Auditory-Verbal Learning Test: Applicability for the Brazilian elderly population. *Revista Brasileira de Psiquiatria (Sao Paulo, Brazil)*, *29*(4), 324–329. https://doi.org/10.1590/S1516-44462006005000053

Mandelman, S. D., & Grigorenko, E. L. (2012). *BDNF* Val66Met and cognition: All, none, or some? A meta-analysis of the genetic association. *Genes Brain & Behavior*, *11*(2), 127–136. https://doi.org/10.1111/j.1601-183X.2011.00738.x

Manolio, T. A., Collins, F. S., Cox, N. J., Goldstein, D. B., Hindorff, L. A., Hunter, D. J., McCarthy, M. I., Ramos, E. M., Cardon, L. R., Chakravarti, A., Cho, J. H., Guttmacher, A. E., Kong, A., Kruglyak, L., Mardis, E., Rotimi, C. N., Slatkin, M., Valle, D., Whittemore, A. S., ... Visscher, P. M. (2009). Finding the missing heritability of complex diseases. *Nature*, *461*(7265), 747–753. https://doi.org/10.1038/nature08494

Molendijk, M. L., Bus, B. A. A., Spinhoven, P., Kaimatzoglou, A., Oude Voshaar, R. C., Penninx, B. W. J. H., van IJzendoorn, M. H., & Elzinga, B. M. (2012). A systematic review and meta-analysis on the association between *BDNF* val66met and hippocampal volume—A genuine effect or a winners curse? *American Journal of Medical Genetics. Part B, Neuropsychiatric Genetics*, *159*(6), 731–740. https://doi.org/10.1002/ajmg.b.32078

Montag, C., Felten, A., Markett, S., Fischer, L., Winkel, K., Cooper, A., & Reuter, M. (2014). The role of the *BDNF* Val66Met polymorphism in individual differences in long-term memory capacity. *Journal of Molecular Neuroscience*, *54*(4), 796–802. https://doi.org/10.1007/s12031-014-0417-1

Mußotter, T., Kluwe, L., Högel, J., Nguyen, R., Cooper, D. N., Mautner, V. F., & Kehrer-Sawatzki, H. (2012). Non-coding RNA ANRIL and the number of plexiform neurofibromas in patients with *NF1* microdeletions. *BMC Medical Genetics*, *13*(1), Article 98. https://doi.org/10.1186/1471-2350-13-98

North, K. (2000). Neurofibromatosis type 1. *American Journal of Medical Genetics*, *97*(2), 119–127. https://doi.org/10.1002/1096-8628(200022)97:2<119:AID-AJMG3>3.0.CO;2-3

Pasmant, E., Vidaud, M., Vidaud, D., & Wolkenstein, P. (2012). Neurofibromatosis type 1: From genotype to phenotype. *Journal of Medical Genetics*, *49*(8), 483–489. https://doi.org/10.1136/jmedgenet-2012-100978

Pemov, A., Sung, H., Hyland, P. L., Sloan, J. L., Ruppert, S. L., Baldwin, A. M., Boland, J. F., Bass, S. E., Lee, H. J., Jones, K. M., Zhang, X., NISC Comparative Sequencing Program, Mullikin, J. C.,

Widemann, B. C., Wilson, A. F., & Stewart, D. R. (2014). Genetic modifiers of neurofibromatosis type 1-associated café-au-lait macule count identified using multi-platform analysis. *PLOS Genetics*, *10*(10), Article e1004575. https://doi.org/10.1371/journal.pgen.1004575

Rey, A. (1941). L'examen psychologique dans les cas d'encephalopathie traumatique. *Archives de Psychologie*, *28*, 112.

Rosselli, M., & Ardila, A. (2003). The impact of culture and education on non-verbal neuropsychological measurements: A critical review. *Brain and Cognition*, *52*(3), 326–333. https://doi.org/10.1016/S0278-2626(03)00170-2

Savitz, J., Solms, M., & Ramesar, R. (2006). The molecular genetics of cognition: Dopamine, COMT and *BDNF*. *Genes Brain & Behavior*, *5*(4), 311–328. https://doi.org/10.1111/j.1601-183X.2005.00163.x

Schwetye, K. E., & Gutmann, D. H. (2014). Cognitive and behavioral problems in children with neurofibromatosis type 1: Challenges and future directions. *Expert Review of Neurotherapeutics*, *14*(10), 1139–1152. https://doi.org/10.1586/14737175.2014.953931

Shilyansky, C., Lee, Y. S., & Silva, A. J. (2010). Molecular and cellular mechanisms of learning disabilities: A focus on NF1. *Annual Review of Neuroscience*, *33*, 221–243. https://doi.org/10.1146/annurev-neuro-060909-153215

Shin, M. S., Park, S. Y., Park, S. R., Seol, S. H., & Kwon, J. S. (2006). Clinical and empirical applications of the Rey–Osterrieth complex figure test. *Nature Protocols*, *1*(2), 892–899. https://doi.org/10.1038/nprot.2006.115

Silva, A. J., Frankland, P. W., Marowitz, Z., Friedman, E., Laszlo, G. S., Cioffi, D., Jacks, T., & Bourtchuladze, R. (1997). A mouse model for the learning and memory deficits associated with neurofibromatosis type I. *Nature Genetics*, *15*(3), 281–284. https://doi.org/10.1038/ng0397-281

Squire, L. R. (2004). Memory systems of the brain: A brief history and current perspective. *Neurobiology of Learning and Memory*, *82*(3), 171–177. https://doi.org/10.1016/j.nlm.2004.06.005

Strauss, E., Sherman, E. M. S., & Spreen, O. (2006). *A compendium of neuropsychological tests: Administration, norms, and commentary* (3rd ed.). Oxford University Press.

Titze, S., Peters, H., Währisch, S., Harder, T., Guse, K., Buske, A., Tinschert, S., & Harder, A. (2010). Differential MSH2 promoter methylation in blood cells of Neurofibromatosis type 1 (NF1) patients. *European Journal of Human Genetics*, *18*(1), 81–87. https://doi.org/10.1038/ejhg.2009.129

van der Vaart, T., Rietman, A. B., Plasschaert, E., Legius, E., Elgersma, Y., & Moll, H. A., & the NF1-SIMCODA Study Group. (2016). Behavioral and cognitive outcomes for clinical trials in children with neurofibromatosis type 1. *Neurology*, *86*(2), 154–160. https://doi.org/10.1212/WNL.0000000000002118

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