Shared executive dysfunctions in unaffected relatives of patients with autism and obsessive-compulsive disorder

Richard Delorme[a,b,*,#], Véronique Goussé[a,*], Isabelle Roy[a,c], Anca Trandafir[c], Flavie Mathieu[a], Marie-Christine Mouren-Siméoni[b], Catalina Betancur[a], Marion Leboyer[a,c]

[a] INSERM U513, Neurobiologie et Psychiatrie, Université Paris XII, Créteil, France

[b] Service de Psychopathologie de l'Enfant et de l'Adolescent, Hôpital Robert Debré, Assistance Publique-Hôpitaux de Paris, Paris, France

[c] Département de Psychiatrie Adulte, Hôpital Henri Mondor et Albert Chenevier, Assistance Publique- Hôpitaux de Paris, Créteil, France

* *Both authors contributed equally to this work.*

Running Head: Executive dysfunctions in autism and OCD

[#]Corresponding author: Richard Delorme, INSERM U513, Faculté de Médecine, 8 rue du Général Sarrail, 94010 Créteil Cedex, France. E-mail: Richard.Delorme@creteil.inserm.fr

Abstract

Background: Executive dysfunctions have been studied as a potential endophenotype associated with the genetic basis of autism. Given that recent findings from clinical and molecular genetic studies suggest that autism and obsessive-compulsive disorder (OCD) could share a common pattern of heritability, we assessed executive functions as a possible common cognitive endophenotype in unaffected family members of individuals with either autism or OCD.

Methods: Five tests assessing executive functions (Tower of London, verbal fluency, design fluency, trail making and association fluency) were proposed to 58 unaffected first-degree relatives (parents and siblings) of probands with autism and 64 unaffected first-degree relatives of OCD patients. Results were compared with those of 47 healthy controls matched for age, sex, and level of education.

Results: In the Tower of London test, both groups of unaffected relatives showed significantly lower scores and longer response times compared with controls. No differences were observed between autism and OCD relatives and healthy controls in the four other tasks (verbal fluency, design fluency, trail making test and association fluency).

Conclusions: Our findings show the existence of executive dysfunction in the unaffected first-degree relatives of probands with OCD, similar to those observed in the relatives of patients with autism. These results support and extend previous cognitive studies on probands indicating executive dysfunctions in autism and OCD. Planning and working memory processes could thus represent a common cognitive endophenotype in autism and OCD that could help in the identification of genes conferring vulnerability to these disorders.

Key words: Endophenotype, Tower of London, Planning, Working memory

1. Introduction

Recent genetic linkage and association studies in autism suggesting the involvement of specific susceptibility loci and genes have elicited considerable interest, but attempts to replicate the initial findings have met with limited success [33]. Because of the clinical, genetic and etiological heterogeneity inherent to autism, the use of additional approaches may facilitate the identification of the susceptibility genes [27]. One such strategy is the endophenotype-based approach. Endophenotypes are variables that correlate with a given disease, are usually sub-clinical, involve fewer genes than those involved in the disease syndrome itself and could assist in the identification of genes conferring vulnerability to the disorder [14]. To meet the criteria for an endophenotype, a marker must be present in affected individuals, has to be heritable and co-segregate with the illness, it should be state-independent (i.e., manifests in an individual whether or not the illness is active), and

must be found among unaffected relatives of patients at a higher rate than in the general population [14, 27].

Results from clinical and molecular genetic studies suggest that autism and obsessive compulsive disorder (OCD) could share a common pattern of heritability. Among a large number of clinical variables evaluated, obsessive-compulsive/repetitive behaviors have been found to be highly correlated among autism probands and their sib-pairs [11, 50, 51], and among autism probands and their first- and second-degree relatives [4, 5, 31, 57]. Furthermore, Hollander *et al*. [20] showed that autistic children with high scores on narrow restricted interests and rituals were significantly more likely to have one or both parents with OCD, especially fathers, than those with low scores. In addition, a recent genome scan in autism showed that the bulk of evidence for linkage to chromosome 1q24 derived from families most severely affected by obsessive-compulsive behaviors [6]. These studies suggest that the identification of an endophenotype in autism could be facilitated by the search of characteristics shared by OCD and autism. One such common feature could be executive dysfunctions.

Impairments in executive functions have been previously reported in patients with autism or OCD. The executive function domain includes skills required to generate and drive on complex strategies, including planning, working memory, inhibition and flexibility. Planning, i.e., the ability to achieve a goal through a series of intermediate steps [37], has been mainly explored with the Tower of London task in probands with autism [18] and in their relatives [21, 22, 39]. These studies provided converging evidence showing that impairments in planning could be part of the broader autism phenotype, defined as the autism-like traits present in relatives of autistic individuals, milder but qualitatively similar to those seen in probands, and considered a manifestation of the genetic liability to autism [9]. Results are less obvious for a deficit of working memory in autism, i.e., the capacity to keep in mind and organize spatial or verbal information, as this process is often embedded in tests of planning and rarely tested alone. Only the study by Hughes *et al.* [21] included a specific task of working memory and found impairments in parents of probands when compared to controls. Inhibition abilities that require the capacity to interrupt motor or verbal responses have also been explored in patients with autism, with most of the studies suggesting that these skills are preserved [38]. Mental flexibility, which refers to the ability to shift to a different thought or action according to the context of situations, has been tested mainly with the Wisconsin Card Sorting Test (WCST). Individuals with autism are highly perseverative in their responses, indicating a lack of flexibility [18]. However, such deficits have not been reported in unaffected first-degree relatives of probands with autism [39, 52].

In OCD, previous studies have shown that patients are not impaired in their general cognitive functioning [12] but more specifically in organizational strategies mostly linked with planning ability [40, 46]. For instance, OCD patients take more time to generate an alternative strategy after an error when performing a computerized version of the Tower of London task [54, 55]. Other executive function domains such as inhibition or flexibility have also been explored but the results remain contradictory [for review see 26]. Most of the studies were limited in size and confounding variables

related to the disorder such as age of onset, medication, comorbidity and severity of the disorder could explain the discrepancies observed. The study of executive functions in the unaffected relatives of OCD probands, which has never been conducted, could help to clarify these divergent results.

Neurocognitive dysfunctions are considered among the most promising candidate endophenotypes in psychiatric disorders [7]. Given that planning deficits are observed both in autism and OCD probands, we hypothesized that executive impairments, specifically in planning, could represent an endophenotype shared by relatives of patients with OCD or autism. To explore this question, we evaluated different components of executive functions in unaffected first-degree relatives of OCD probands and in first-degree relatives of patients with autism, and compared them to a group of sex-, age-, and educational level-matched healthy controls.

2. Subjects and methods

2.1. Subjects

Unaffected parents and siblings of probands with autism or OCD were asked to participate in the study. Relatives were directly interviewed by experienced psychiatrists using the French version of the Diagnostic Interview for Genetic Studies (DIGS) [35] or the Schedule for Affective Disorders and Schizophrenia for School Age Children - epidemiological version (KIDDIE-SADS-e) [36], to confirm the absence of current mood disorder or substance abuse/dependence at time of inclusion and the lack of lifetime schizophrenia or OCD. Also, a non structured interview was conducted by clinicians with expertise in autism spectrum disorders to exclude relatives suffering from autism spectrum disorders. Finally, to be included, relatives could not have been receiving psychotropic treatment at the time of assessment. The sample was composed of 58 unaffected relatives (18 fathers, 21 mothers, 9 brothers, and 10 sisters) of 23 patients with autism and 64 unaffected relatives (25 fathers, 28 mothers, 5 brothers, and 6 sisters) of 30 OCD patients. Demographic characteristics of the relatives included are presented in Table 1.

The probands of the relatives were recruited at two university hospital psychiatric departments for children (Hôpital Robert Debré, Paris) and adults (Hôpital Albert Chenevier, Créteil). Probands had to fulfill DSM-IV criteria for autistic disorder or OCD (American Psychiatric Association 1994). The diagnosis of autism was confirmed with the Autism Diagnostic Interview-Revised (ADI-R) [29]. Probands with autism were included after a medical workup including karyotype, molecular testing for fragile X syndrome, and metabolic screening. Subjects demonstrated to suffer from medical conditions associated with autism, such as fragile X syndrome or chromosomal abnormalities were excluded from the study. Among the 23 patients with autism whose relatives were assessed, there were 13 males and 10 females, with a mean age of 21.2 ± 6.8 years (range 10-36 years); 18 were non verbal and had moderate to severe mental retardation and 5 had mild mental retardation, with a relatively preserved language. Probands with OCD were evaluated by a direct clinical interview with either the DIGS for patients over the age of 15 years, or the KIDDIE-SADS-e for patients aged less

than 15 years. Among the 30 OCD patients whose relatives were assessed, there were 14 males and 16 females, with a mean age of 23.4 ± 12.5 years (range 10-42 years).

Controls (n=47) were healthy volunteers recruited among blood donors at the Pitié-Salpêtrière Hospital (Paris) for those aged over 18 years (n=39) and through advertisement at a local middle school for younger subjects (n=8). Adult controls were included after being interviewed with the DIGS to confirm the absence of lifetime personal history of psychiatric disorders. Subjects younger than 18 years were interviewed with the French version of the Mini-International Neuropsychiatric Interview (MINI-Kid) [49] to confirm the absence of lifetime psychiatric disorders. In addition, questions adapted from the Family Interview for Genetic Studies (FIGS) [30] were asked to the healthy volunteers to confirm the absence of family history of psychiatric disorders in first- and second-degree relatives. Control subjects were receiving no psychotropic treatment at the time of assessment. Demographic characteristics of the control group are presented in Table 1. When compared to the group of relatives, controls did not differ for age (Kruskall Wallis, χ^2 =2.04, df=2, p=0.36), gender (Kruskall Wallis, χ^2 = 0.84, df=2, p= 0.65) or education level (Pearson, χ^2 = 0.26, df=2, p= 0.87).

All unaffected relatives and controls had to be from European descent and French speaking to be included in the study. The local Research Ethics Board approved the study protocol. Written informed consent was obtained from all participating subjects. If the proband was under 18 years old, the proband's consent and written parental consent were obtained.

2.2. Cognitive tasks

All participants were tested individually by an experienced psychologist. Five neuropsychological tests assessing various components of executive functions were carried out in the same order for all subjects. The first test performed was the *Tower of London task* [48], requiring planning and spatial working memory [25]. The participant was asked to rearrange the three disks placed on three different pegs, drawn at the bottom of a paper sheet, so that they matched the positions of the goal state shown on top. There was no way of manipulating the material so the subject had to solve the problem mentally. The participant was given a set of two-, three-, four- and five-move problems presented randomly. This task was divided into two levels of difficulty: 'easy' problems (two and three moves) and 'difficult' problems (four and five moves) [21]. The subject's performance on this task was measured by the number of correct solutions given for each level of difficulty (six items for each level) and the time taken to solve each problem.

The second test carried out was the *Trail Making test* [44]. We used part B of this test, which assesses flexibility and mental set shifting [28]. The subject had to draw a continuous line to alternately connect the digits 1 to 13 and the letters A to L on a sheet of paper. The time taken to complete the task was recorded.

The third test proposed was the *Design Fluency task* [23]. The 'fixed condition' was used, which requires productivity and flexibility on a spatial material [10]. Subjects were asked to generate as

many different figures as possible in three minutes, using two vertical parallel lines, one large white circle and one small black circle. The number of correct figures generated was noted and clusters of similar drawings were counted.

The fourth test was the *Verbal Fluency task* [3], which assesses productivity and flexibility on a verbal material [53]. The participant was asked to generate as many words as possible beginning with a specified letter (f, a, or s) within three minutes. The number of correct words was noted (excluding errors and repetitions) as were 'phonemic clusters' (groups of words beginning or ending with the same two letters and homonyms).

The last and fifth test was the *Association Fluency task*. This test was specifically designed by our research team to measure the capacity of subjects to produce a list of associated words after being presented with an initial word. The specificity of this last test is the absence of cues (i.e., a letter or a name of category), thus requiring the subject to use his imagination. Each subject was given three minutes to produce as many words as possible after the presentation of a word ('house', 'airplane' and 'camel'); the test was repeated three times, once for each word.

2.3. Statistical analysis

Because the observed distribution of continuous variables was not normal in the groups of unaffected relatives and controls, inter-group comparisons were made with a nonparametric test, the Kruskal Wallis test. For non-continuous variables, the Pearson χ^2 test was used. To test diagnostic specificity, pair-wise comparisons were performed with the nonparametric Mann-Whitney U test. All relatives and controls completed all the tests, thus the number of subjects included in all the comparisons was the same. All p values are nominal and not corrected for multiple testing.

3. Results

Mean performances on executive function tests for both groups of unaffected relatives and for controls are summarized in Table 2. Among the five tests assessing executive functions, inter-group comparisons with the Kruskall-Wallis test revealed significant differences between unaffected relatives of probands with OCD, unaffected relatives of probands with autism, and controls only for the Tower of London task. Differences were observed for the total score, as well as the scores for the first and the second level of difficulty. Significant differences among the three groups were also observed for the total response times and the response times of the first and second level of difficulty of the test. By contrast, no significant differences were observed among the three groups in terms of reaction time in the Trail Making test, number of drawings and clusters in the Design Fluency test, number of words and clusters during the Verbal Fluency test, and number of words produced during the Association Fluency test.

Pair-wise comparisons of the number of responses on the Tower of London task revealed that relatives of probands with autism gave fewer correct answers than controls during the first and the second levels of difficulty of the task, so the total number of correct solutions was also significantly

lower. Furthermore, the relatives of individuals with autism took significantly more time than controls during the first and second levels of difficulty; the total response time was also significantly higher in the autism relatives than in controls.

Similar abnormalities were observed when comparing the number of responses in the unaffected relatives of subjects with OCD to controls. The OCD relatives gave fewer correct answers for both levels of difficulty of the Tower of London task when compared to controls, and the total score was also lower. In addition, the relatives of OCD probands took more time than controls on the first level of the test, but not on the second level or total response times.

Finally, the pair-wise comparison of the two groups of relatives for the first level of the test (for which both groups took more times to solve problems) did not reveal any significant differences ($U= 1671$, $p=0.34$). Furthermore, no difference was observed between the two groups concerning the number of correct answers given, whatever the level of the task performed (first level, $U= 1788$, $p=0.70$; second level, $U= 1812$, $p=0.82$; entire task, $U= 1802$, $p=0.79$).

4. Discussion

Neurocognitive dysfunctions, specifically executive impairments, were tested as putative shared abnormalities in unaffected relatives of patients with OCD and autism. Our study revealed that both groups of relatives performed significantly worse than controls on the Tower of London task. To our knowledge, this is the first study to report executive dysfunctions in unaffected relatives of OCD patients. We suggest that these dysfunctions could be a characteristic shared by the unaffected relatives of patients with OCD and autism. Thus, specific executive processes, such as planning and spatial working memory, could aggregate in these families and might be a heritable component of OCD and autism. These specific executive traits might be used as endophenotypes to dissect the genetic complexity of both disorders. Furthermore, our findings contribute to a growing body of evidence suggesting a relationship between OCD and autism.

4.1. Executive dysfunctions in autism and OCD

Impairments in executive functions have been commonly reported in autism [41]. Although a few studies have failed to observe deficits in autistic subjects [e.g., 8, 16], this could be a function of the tests used. Probands of all ability ranges have been found to be disturbed, especially in planning and working memory [18]. The same dysfunctions have been reported in their unaffected relatives, with impairments commonly observed in the Tower of London task [21, 22, 39]. The very significant differences in terms of performances and response times we obtained on this test between first-degree relatives of individuals with autism and controls, regardless of the level of difficulty, further strengthen that these executive processes belong to the broader autism phenotype [18, 37]. The heritability of deficits in planning, which is suggested by the familial aggregation, could represent one of the most important heritable components of autism [9].

In OCD, fewer reports have explored cognitive functions in probands, but executive dysfunctions have been observed [26]. The difficulties to solve problems in the Tower of London task that we observed in the unaffected relatives of individuals with OCD reinforce several studies in probands suggesting planning and working memory dysfunctions [15, 42, 43, 54, 55]. A recent study using a computerized version of the Tower of London task to compare OCD patients with controls found results similar to those we obtained in relatives of subjects with OCD: a lengthened time to answer the conditions requiring one or two moves and decreased performance scores whatever the level of difficulty of the task [54]. Interestingly, this same study showed that independently from the severity of the illness, OCD patients show decreased frontal-striatal responsiveness during planning, mainly in the dorsolateral prefrontal cortex and caudate nucleus [54]. The state-independent nature of these abnormalities, their neuro-anatomical correlates, and their familial aggregation, reinforce the hypothesis that planning deficit could be an endophenotype in OCD.

4.2. Executive dysfunctions as a shared characteristic of OCD and autism

Despite results from clinical and molecular genetic studies suggesting that autism and OCD could share genetic factors, it is surprising that symptomatically so different disorders could both be linked to the same cognitive and/or neural dysfunctions. One possibility is that even if both groups of relatives performed worse than healthy controls on the Tower of London task, they carried out the task in different ways. For example, given that OCD is an anxiety disorder, it is conceivable that the relatives of OCD probands made more errors or took longer time during the task because they were more worried about their performance. By contrast, as autism involves a preference for rule systems, it is also conceivable that parents of individuals with autism may have spent more time wanting to run through different permutations in their mind to see how this would lead to different outcomes, and thus took more time to fulfill the task. Thus, the same pattern of performance in both groups of relatives could be underlined by different cognitive ‘styles’.

Another explanation could be that the executive dysfunction observed in OCD and autism could depend on a specific clinical feature shared by both disorders. Specifically, repetitive behaviors constitute a core symptom observed in OCD as well as in autism. A criterion for autism diagnosis is the presence of rigid and repetitive behaviors, restricted interests and marked resistance to change. A preliminary study reported that children with autism who had a higher total score on the repetitive domain of the ADI-R had significantly more often one or both parents with OC traits or disorder, compared with those who had a low score [20]. Moreover, a recent study reported similar frequencies of OC symptoms in OCD and Asperger syndrome [45]. In addition, Hollander *et al*. [19] reported that high ADI repetitive behavior scores are strongly correlated with increased volume of the right caudate in individuals with autism. Since large caudate volumes have also been described in adults with OCD [47], possible common pathways associated with repetitive behaviors in OCD and autism could exist [19].

4.3. Executive dysfunction as a specific component of OCD and autism?

As in OCD and autism, executive dysfunctions have been found to aggregate in families of individuals with schizophrenia or bipolar disorder [17, 24]. Therefore, the specificity of the cognitive dysfunctions observed in this study remains to be clarified. The five different tests that were proposed in this study tried to explore further the specificity of executive processes related to OCD and/or autism. Only the Tower of London task showed highly significant differences between relatives of both proband groups and controls. One explanation could be the task complexity, the Tower of London task being considered as the most difficult task of our study. However, our results showed that both groups of relatives performed less well than controls even in the easiest level of the task. A better explanation could be that none of the other tests implicates the simultaneous participation of planning and spatial working memory processes (i.e., organization and manipulation of visual mental images). Finally, as recently suggested by Goldberg & Weinberger [13], behavioral measures used alone might be insufficiently discriminative to further explore the specificity and the complexity of cognitive processes implicated in psychiatric phenotypes. Thus, to improve the exploration of the cognitive processes shared by autism and OCD and their neuro-anatomic correlates, it would be useful to replicate our findings associating cognitive tasks and functional neuro-imaging.

4.4. Limitations

There are several limitations to our study that need to be considered when interpreting our current findings. As in previous family studies that explored executive functions in autism [21] or schizophrenia [24], both groups of relatives and controls were matched on the education level and not on a general measure of intelligence (IQ). Although some studies analyzing the association between executive functions and IQ found few or no correlations between WISC [1, 2] or WAIS subtests [56] and executive tests, it is usually admitted that IQ is correlated with performance on executive functions. Thus, it would be necessary to further control the potential impact of intellectual functioning between groups by the use of a test measuring IQ in additional works. However, due to the restricted size of the groups in the present study, it seems improbable that, whatever the strategy used, we can rule out a confounding effect of IQ on our results.

A second limitation concerns how we determined that relatives of autism and OCD patients were affected or not. It is well known that phenotypes are more dimensional than categorical in autism [31] as well as in OCD [32]. Although numerous studies have tried to better define the broader phenotype of autism [9] or OCD [34], the candidate traits to describe these broad phenotypes remain uncertain. Thus, the exclusion criteria for the relatives in our study were based on a narrow phenotype as described in the DSM-IV, i.e., presence of full criteria for OCD or for one of the autism spectrum disorders.

A third limitation is that the sample of probands with autism was not representative of the sex ratio characteristic of this disorder (1 female:4 males), as almost half of them were female. Even if no relation has ever been demonstrated between the gender of the probands and the cognitive

performances in autism relatives, this characteristic of our data set could restrict the generalization of our findings.

Finally, the use of "super-normal" controls (without personal or family history of psychiatric disorders) could generate a bias if we hypothesize that they could carry protective genetic factors for psychiatric disorders. If this were true, then part of our results could be due to these protective factors in the controls and not to the vulnerability factors for executive dysfunctions present in relatives. However, this possibility seems unlikely, given that previous studies have found results similar to ours when studying the usual control populations.

5. Conclusion

On the basis of the present results, we conclude that deficits in planning and spatial working memory processes aggregate in families of probands with OCD and autism and might constitute a shared intermediate cognitive phenotype. Further work is required to confirm our findings in relatives of OCD patients. If such studies confirm that specific executive dysfunctions aggregate in both types of families, the assessment of this cognitive domain could become an important quantitative trait in alternative phenotypic strategies for genetic studies of autism and OCD. Such assessments could also improve our understanding of the developmental mechanisms underlying executive dysfunctions in affected patients and unaffected relatives.

Acknowledgements

We thank the patients and the families who participated in this study. This work was supported by grants from Assistance Publique-Hôpitaux de Paris (CRC and PHRC AOM95076), Fondation pour la Recherche Médicale, INSERM, Ministère de la Recherche (contrat Cognitique) and Fondation de France.

References

[1] Ardila A, Galeano LM, Rosselli M. Toward a model of neuropsychological activity. Neuropsychol Rev 1998;8:171-90.

[2] Ardila A, Pineda D, Rosselli M. Correlation between intelligence test scores and executive function measures. Arch Clin Neuropsychol 2000;15:31-6.

[3] Benton A L (1968). Differential behavioral effects in frontal lobe disease. Neuropsychologia 6, 53-60.

[4] Bolton P, Macdonald H, Pickles A, Rios P, Goode S, Crowson M, et al. A case-control family history study of autism. J Child Psychol Psychiatry 1994;35:877-900.

[5] Bolton PF, Pickles A, Murphy M, Rutter M. Autism, affective and other psychiatric disorders: patterns of familial aggregation. Psychol Med 1998;28:385-95.

[6] Buxbaum JD, Silverman J, Keddache M, Smith CJ, Hollander E, Ramoz N, et al. Linkage analysis for autism in a subset families with obsessive-compulsive behaviors: evidence for an autism susceptibility gene on chromosome 1 and further support for susceptibility genes on chromosome 6 and 19. Mol Psychiatry 2004;9:144-50.

[7] Cornblatt BA, Malhotra AK. Impaired attention as an endophenotype for molecular genetic studies of schizophrenia. Am J Med Genet 2001;105:11-5.

[8] Dawson G, Munson J, Estes A, Osterling J, McPartland J, Toth K, Carver L, Abbott R. Neurocognitive function and joint attention ability in young children with autism spectrum disorder versus developmental delay. Child Dev 2002;73:345-58.

[9] Dawson G, Webb S, Schellenberg GD, Dager S, Friedman S, Aylward E, et al. Defining the broader phenotype of autism: genetic, brain, and behavioral perspectives. Dev Psychopathol 2002;14:581-611.

[10] Demakis GJ, Harrison DW. Relationships between verbal and nonverbal fluency measures: implications for assessment of executive functioning. Psychol Rep 1997;81:43-8.

[11] Folstein SE, Santangelo SL, Gilman SE, Piven J, Landa R, Lainhart J, et al. Predictors of cognitive test patterns in autism families. J Child Psychol Psychiatry 1999;40:1117-28.

[12] Galderisi S, Mucci A, Catapano F, D'Amato AC, Maj M. Neuropsychological slowness in obsessive-compulsive patients. Is it confined to tests involving the fronto-subcortical systems? Br J Psychiatry 1995;167:394-8.

[13] Goldberg TE, Weinberger DR. Genes and the parsing of cognitive processes. Trends Cogn Sci 2004;8:325-35.

[14] Gottesman II, Gould TD. The endophenotype concept in psychiatry: etymology and strategic intentions. Am J Psychiatry 2003;160:636-45.

[15] Goussé V, Delorme R, Chabane N, Perez-Diaz F, Mathieu F, Mouren-Siméoni MC, et al. Is age at onset associated with executive dysfunction in obsessive-compulsive disorder? Encéphale 2005;31:666-71.

[16] Griffith EM, Pennington BF, Wehner EA, Rogers SJ. Executive functions in young children with autism. Child Dev 1999;70:817-32.

[17] Hasler G, Drevets WC, Manji HK, Charney DS. Discovering endophenotypes for major depression. Neuropsychopharmacology 2004;29:1765-81.

[18] Hill EL. Executive dysfunction in autism. Trends Cogn Sci 2004;8:26-32.

[19] Hollander E, Anagnostou E, Chaplin W, Esposito K, Haznedar MM, Licalzi E, et al. Striatal volume on magnetic resonance imaging and repetitive behaviors in autism. Biol Psychiatry 2005;58:226-32.

[20] Hollander E, King A, Delaney K, Smith CJ, Silverman JM. Obsessive-compulsive behaviors in parents of multiplex autism families. Psychiatry Res 2003;117:11-6.

[21] Hughes C, Leboyer M, Bouvard M. Executive function in parents of children with autism. Psychol Med 1997;27:209-20.

[22] Hughes C, Plumet MH, Leboyer M. Towards a cognitive phenotype for autism: increased prevalence of executive dysfunction and superior spatial span amongst siblings of children with autism. J Child Psychol Psychiatry 1999;40:705-18.

[23] Jones-Gotman M, Milner B. Design fluency: the invention of nonsense drawings after focal cortical lesions. Neuropsychologia 1977;15:653-74.

[24] Kathmann N, Hochrein A, Uwer R, Bondy B. Deficits in gain of smooth pursuit eye movements in schizophrenia and affective disorder patients and their unaffected relatives. Am J Psychiatry 2003;160:696-702.

[25] Keith Berg W, Byrd D. The Tower of London spatial problem-solving task: enhancing clinical and research implementation. J Clin Exp Neuropsychol 2002;24:586-604.

[26] Kuelz AK, Hohagen F, Voderholzer U. Neuropsychological performance in obsessive-compulsive disorder: a critical review. Biol Psychol 2004;65:185-236.

[27] Leboyer M. Searching for alternative phenotypes in psychiatric genetics. Methods Mol Med 2003;77:145-61.

[28] Lezack MD. Lezack, Neuropsychological Assessment. 3rd ed. New York: Oxford University Press; 1995.

[29] Lord C, Rutter M, Le Couteur A. Autism Diagnostic Interview-Revised: a revised version of a diagnostic interview for caregivers of individuals with possible pervasive developmental disorders. J Autism Dev Disord 1994;24:659-85.

[30] Maxwell ME. Family Interview for Genetic Studies. Clinical Neurogenetic Branch, Intramural Research Program, NIMH 1992.

[31] Micali N, Chakrabarti S, Fombonne E. The broad autism phenotype: findings from an epidemiological survey. Autism 2004;8:21-37.

[32] Miguel EC, Leckman JF, Rauch S, do Rosario-Campos MC, Hounie AG, Mercadante MT, Chacon P, et al. Obsessive-compulsive disorder phenotypes: implications for genetic studies. Mol Psychiatry 2005;10:258-75.

[33] Muhle R, Trentacoste SV, Rapin I. The genetics of autism. Pediatrics. 2004;113:472-86.

[34] Nestadt G, Addington A, Samuels J, Liang KY, Bienvenu OJ, Riddle M, et al. The identification of OCD-related subgroups based on comorbidity. Biol Psychiatry 2003;53:914-920.

[35] Nurnberger JI Jr, Blehar MC, Kaufmann CA, York-Cooler C, Simpson SG, Harkavy-Friedman J, et al. Diagnostic interview for genetic studies. Rationale, unique features, and training. NIMH Genetics Initiative. Arch Gen Psychiatry. 1994;51:849-59.

[36] Orvaschel H, Puig-Antich J, Chambers W, Tabrizi MA, Johnson R. Retrospective assessment of prepubertal major depression with the Kiddie-SADS-e. J Am Acad Child Psychiatry. 1982;21:392-7.

[37] Ozonoff S, Cook I, Coon H, Dawson G, Joseph RM, Klin A, et al. Performance on Cambridge Neuropsychological Test Automated Battery subtests sensitive to frontal lobe function in people with autistic disorder: evidence from the Collaborative Programs of Excellence in Autism network. J Autism Dev Disord 2004;34:139-50.

[38] Ozonoff S, Jensen J. Brief report: specific executive function profiles in three neurodevelopmental disorders. J Autism Dev Disord 1999;29:171-7.

[39] Ozonoff S, Rogers SJ, Farnham JM, Pennington BF. Can standard measures identify subclinical markers of autism? J Autism Dev Disord 1993;23:429-41.

[40] Penades R, Catalan R, Andres S, Salamero M, Gasto C. Executive function and nonverbal memory in obsessive-compulsive disorder. Psychiatry Res 2005;133:81-90.

[41] Pennington BF, Ozonoff S. Executive functions and developmental psychopathology. J Child Psychol Psychiatry 1996;37:51-87.

[42] Purcell R, Maruff P, Kyrios M, Pantelis C. Cognitive deficits in obsessive-compulsive disorder on tests of frontal-striatal function. Biol Psychiatry 1998;43:348-57.

[43] Purcell R, Maruff P, Kyrios M, Pantelis C. Neuropsychological deficits in obsessive-compulsive disorder: a comparison with unipolar depression, panic disorder, and normal controls. Arch Gen Psychiatry 1998;55:415-23.

[44] Reitan M, Wolfson D. The Halstead-Reitan Neuropsychological Test Battery. Tucson: Neuropsychology Press; 1985.

[45] Russell AJ, Mataix-Cols D, Anson M, Murphy DG. Obsessions and compulsions in Asperger syndrome and high-functioning autism. Br J Psychiatry 2005;186:525-8.

[46] Savage CR, Baer L, Keuthen NJ, Brown HD, Rauch SL, Jenike MA. Organizational strategies mediate nonverbal memory impairment in obsessive-compulsive disorder. Biol Psychiatry. 1999;45:905-16.

[47] Scarone S, Colombo C, Livian S, Abbruzzese M, Ronchi P, Locatelli M, et al. Increased right caudate nucleus size in obsessive-compulsive disorder: detection with magnetic resonance imaging. Psychiatry Res 1992;45:115-21.

[48] Shallice T. Specific impairments of planning. Philos Trans R Soc Lond B Biol Sci 1982;298:199-209.

[49] Sheehan DV, Lecrubier Y, Sheehan KH, Amorim P, Janavs J, Weiller E, et al. The Mini-International Neuropsychiatric Interview (M.I.N.I.): the development and validation of a structured diagnostic psychiatric interview for DSM-IV and ICD-10. J Clin Psychiatry 1998;59:22-33.

[50] Silverman JM, Smith CJ, Schmeidler J, Hollander E, Lawlor BA, Fitzgerald M, et al. Symptom domains in autism and related conditions: evidence for familiality. Am J Med Genet 2002;114:64-73.

[51] Spiker D, Lotspeich L, Kraemer HC, Hallmayer J, McMahon W, Petersen PB, et al. Genetics of autism: characteristics of affected and unaffected children from 37 multiplex families. Am J Med Genet 1994;54:27-35.

[52] Szatmari P, Jones MB, Tuff L, Bartolucci G, Fisman S, Mahoney W. Lack of cognitive impairment in first-degree relatives of children with pervasive developmental disorders. J Am Acad Child Adolesc Psychiatry 1993;32:1264-73.

[53] Troyer AK, Moscovitch M, Winocur G, Alexander MP, Stuss D. Clustering and switching on verbal fluency: the effects of focal frontal- and temporal-lobe lesions. Neuropsychologia 1998;36:499-504.

[54] Van den Heuvel OA, Veltman DJ, Groenewegen HJ, Cath DC, van Balkom AJ, van Hartskamp J, et al. Frontal-striatal dysfunction during planning in obsessive-compulsive disorder. Arch Gen Psychiatry 2005;62:301-9.

[55] Veale DM, Sahakian BJ, Owen AM, Marks IM. Specific cognitive deficits in tests sensitive to frontal lobe dysfunction in obsessive-compulsive disorder. Psychol Med 1996;26:1261-9.

[56] Welsh MC, Labbe EE, Delayney D. Cognitive strategies and personality variables in adherence to exercise. Psychol Rep 1991;68:1327-35.

[57] Wilcox JA, Tsuang MT, Schnurr T, Baida-Fragoso N. Case-control family study of lesser variant traits in autism. Neuropsychobiology 2003;47:171-7.

Table 1. Demographic characteristics of unaffected relatives of patients with autism or obsessive compulsive disorder, and healthy controls

	Unaffected relatives		**Healthy Controls**
	Autism (n=58)	Obsessive compulsive disorder (n=64)	(n=47)
Gender			
Male	28 (49%)	30 (55%)	26 (55%)
Female	30 (51%)	34 (45%)	21 (45%)
Age (years)[a]	38.72 ± 17.9	42.31 ± 15.0	38.0 ± 18.2
Education level[b]			
< 11 years	20 (43%)	40 (50%)	15 (38%)
≥ 11 years	25 (47%)	28 (50%)	24 (61%)

Kruskall Wallis test and Pearson χ^2 test indicated no significant differences among groups for age (Kruskal Wallis, $\chi^2 = 2.04$, 2 df, p=0.36), gender (Kruskal Wallis, $\chi^2 = 0.84$, 2 df, p= 0.65) and education level (Pearson, $\chi^2 = 0.26$, 2 df, p= 0.87).

[a] Mean ± SD.

[b] Education level was considered as a dichotomous variable: less than 11 years of schooling versus 11 or more years of schooling (equivalent to a high school diploma) and was calculated only for subjects older than 18 years.

Table 2. Mean performances in cognitive tests in unaffected relatives of patients with autism or obsessive compulsive disorder, and controls[a]

Test	Unaffected relatives		Healthy Controls
	Autism (n=58)	Obsessive compulsive disorder (n=64)	(n=47)
Tower of London			
Scores			
Total	9.02 ± 2.17 $^{\#\#}$	9.03 ± 1.68 §§§	10.28 ± 1.09 ***
Level 1	5.38 ± 0.91 $^{\#}$	5.38 ± 0.82 §§	5.74 ± 0.44 *
Level 2	3.53 ± 1.79 $^{\#\#}$	3.69 ± 1.35 §§§	4.53 ± 0.99 **
Response time (sec.)			
Total	234.53 ± 7.03 $^{\#\#\#}$	203.59 ± 14.73	168.36 ± 69.96 **
Level 1	61.09 ± 37.01 $^{\#\#\#}$	55.81 ± 37.36 §§	41.70 ± 29.46 **
Level 2	173.98 ± 78.22 $^{\#\#}$	147.78 ± 88.24	126.66 ± 52.77 **
Trail Making			
Response time (sec.)	96.43 ± 40.01	88.75 ± 36.72	89.06 ± 45.31
Design Fluency			
Number of figures	11.71 ± 5.26	13.72 ± 5.98	13.26 ± 4.97
Number of clusters	8.95 ± 4.87	10.11 ± 4.57	9.69 ± 4.99
Verbal Fluency			
Number of words	47.36 ± 19.41	51.45 ± 16.98	53.66 ± 19.39
Number of clusters	29.02 ± 13.51	32.41 ± 11.52	32.54 ± 12.00
Association Fluency			
Number of words	39.40 ± 21.11	44.70 ± 20.77	48.40 ± 22.53

Data represent mean ± SD. Inter-group comparisons were made with the Kruskal Wallis test; * $p<0.05$, ** $p<0.01$, *** $p<0.001$. Pair-wise comparisons were made with the Mann-Whitney test; autism vs. controls, $^{\#}$ $p<0.05$, $^{\#\#}$ $p<0.01$, $^{\#\#\#}$ $p<0.001$; OCD vs. controls, § $p<0.05$, §§ $p<0.01$, §§§ $p<0.001$.