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Assessing the molecular genetics of attention networks

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Abstract

Background: Current efforts to study the genetic underpinnings of higher brain functions have been lacking appropriate phenotypes to describe cognition. One of the problems is that many cognitive concepts for which there is a single word (e.g. attention) have been shown to be related to several anatomical networks. Recently, we have developed an Attention Network Test (ANT) that provides a separate measure for each of three anatomically defined attention networks.

Results: In this study we have measured the efficiency of neural networks related to aspects of attention using the ANT in a population of 200 adult subjects. We then examined genetic polymorphisms in four candidate genes (DRD4, DAT, COMT and MAOA) that have been shown to contribute to the risk of developing various psychiatric disorders where attention is disrupted. We find modest associations of several polymorphisms with the efficiency of executive attention but not with overall performance measures such as reaction time.

Conclusions: These results suggest that genetic variation may underlie inter-subject variation in the efficiency of executive attention. This study also shows that genetic influences on executive attention may be specific to certain anatomical networks rather than affecting performance in a global or non-specific manner. Lastly, this study further validates the ANT as an endophenotypic assay suitable for assessing how genes influence certain anatomical networks that may be disrupted in various psychiatric disorders.

Background

Dopamine transporter (DAT1)

Catecholamine-O-methyl transferase (COMT)

Table 1: Summary ANT values for large mixed population of normal subjects Summary means and standard deviations of attention network scores (ms) and overall reaction time.

Alerting	Orienting	Executive	Reaction Time
36 ± 22	55 ± 27	95 ± 43	540 ± 86

DRD4

COMT

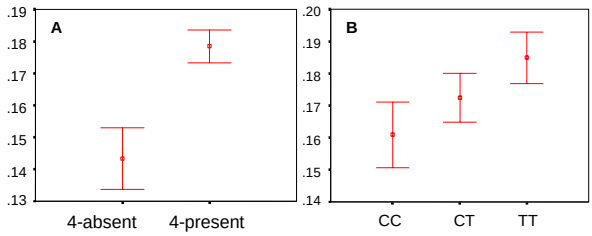

Figure 1
DRD4 and executive attention The Y-axis shows normalized executive attention scores (mean ± SE). The X-axis shows distributions for each genotypic class. Panel A shows the distribution of executive attention score as a function of exon III VNTR genotype in the 4-repeat absent vs. 4-repeat present groups. Panel B shows distribution of executive attention score as a function of a single nucleotide genotype (CC, CT and TT) at position -521.

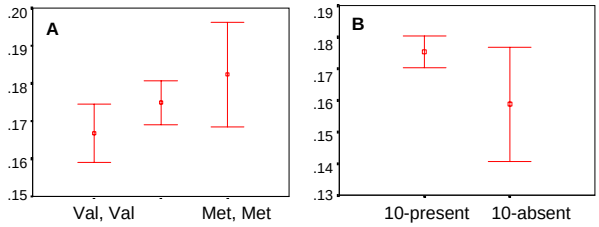

Figure 2
COMT and DAT1 and executive attention Distributions of COMT and DAT1 genotypes vs. executive attention score. The Y-axis shows normalized executive attention scores (mean + SE). The X-axis shows the distribution for each genotypic class. Panel A shows the executive attention scores for each genotypic class at the COMT Valine 108/158 Methionine polymorphism. Panel B shows the relationship between normalized executive attention scores and genotypes at the DAT1 3' UTR repeat polymorphism.

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DAT1

MAOA

Comparison of 'high' vs. 'low' dopamine alleles

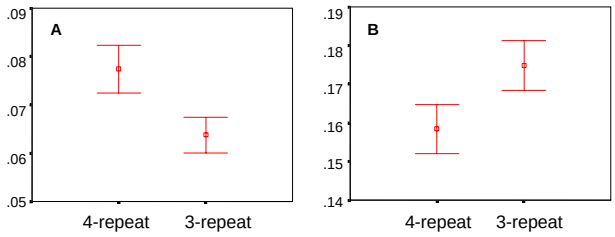

Figure 3
MAOA and alerting and executive attention Distributions of MAOA-LPR genotypes vs. alerting (Panel A) and executive attention (Panel B) scores. The Y-axis shows normalized alerting or executive attention scores (mean + SE). The X-axis shows the distribution for each genotypic class at the repeat polymorphism in the promoter of MAOA. Genotypic classes are a combination of males and females however only homozygous females were chosen, given the random nature of X-chromosome inactivation.

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Discussion

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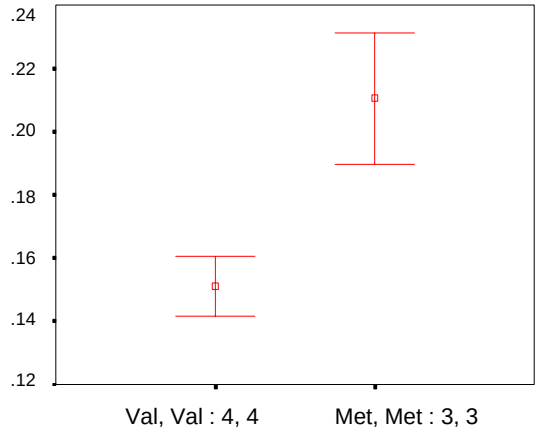

Figure 4
Effect of 'high' vs. 'low' dopamine alleles on executive attention Comparison of normalized executive attention scores in genotypic classes expected to show high and low levels of dopamine. The Y-axis shows normalized executive attention scores (mean + SE). From the entire population, 30 subjects carried the COMT (Val, Val) and MAOA-LPR (4-repeat, 4-repeat) genotypes and are expected to have relatively lower dopamine levels than 20 subjects who carried the COMT (Met, Met) and MAOA-LPR (3-repeat, 3-repeat) genotypes. These distributions are referred to as 'low' dopamine and 'high' dopamine and are shown above.

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Recommendations for molecular genetic studies on the ANT

Conclusions

Methods

Subjects

Behavioral data

Calculation of attention network efficiencies

Genetic sample collection and genotyping methods

Statistical analysis of genetic vs. behavioral variation

Authors' contributions

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References

1. Geyer MA, Braff DL: **Startle habituation and sensorimotor gating in schizophrenia and related animal models.** *Schizophr Bull* 1987, **13:**643-68
2. Matthysse S, Holzman PS, Lange K: **The genetic transmission of schizophrenia: application of Mendelian latent structure analysis to eye tracking dysfunctions in schizophrenia and affective disorder.** *J Psychiatr Res* 1986, **20:**57-67
3. Pantelis C, Barber FZ, Barnes TR, Nelson HE, Owen AM, Robbins TW: **Comparison of set-shifting ability in patients with chronic schizophrenia and frontal lobe damage.** *Schizophr Res* 1999, **37:**251-70
4. Carter CS, Perlstein W, Ganguli R, Brar J, Mintun M, Cohen JD: **Functional hypofrontality and working memory dysfunction in schizophrenia.** *Am J Psychiatry* 1998, **155:**1285-7
5. Swaab-Barneveld H, de Sonneville L, Cohen-Kettenis P, Gielen A, Buitelaar J, Van Engeland H: **Visual sustained attention in a child psychiatric population.** *J Am Acad Child Adolesc Psychiatry* 2000, **39:**651-9
6. Townsend J, Courchesne E, Covington J, Westerfield M, Harris NS, Lyden P, Lowry TP, Press GA: **Spatial attention deficits in patients with acquired or developmental cerebellar abnormality.** *J Neurosci* 1999, **19:**5632-43
7. Parasuraman R, Greenwood PM, Haxby JV, Grady CL: **Visuospatial attention in dementia of the Alzheimer type.** *Brain* 1992, **115:**711-33
8. NIMH: **Genetics and Mental Disorders: Report of the NIMH's Genetics Workgroup.** *In: Book Genetics and Mental Disorders: Report of the NIMH's Genetics Workgroup (Editor ed.^eds.). City* 1999 [http://www.nimh.nih.gov/publist/984268.htm]
9. Faraone SV, Seidman LJ, Kremen WS, Toomey R, Pepple JR, Tsuang MT: **Neuropsychological functioning among the nonpsychotic relatives of schizophrenic patients: a 4-year follow-up study.** *J Abnorm Psychol* 1999, **108:**176-81
10. Falconer: **Introduction to Quantitative Genetics.** *Harlow Essex: Addison Wesley Longman Ltd.* 1996
11. Cornblatt BA, Risch NJ, Faris G, Friedman D, Erlenmeyer-Kimling L: **The Continuous Performance Test, identical pairs version (CPT-IP): I. New findings about sustained attention in normal families.** *Psychiatry Res* 1988, **26:**223-38
12. Bartfai A, Pedersen NL, Asarnow RF, Schalling D: **Genetic factors for the span of apprehension test: a study of normal twins.** *Psychiatry Res* 1991, **38:**115-24
13. Myles-Worsley M, Coon H: **Genetic and developmental factors in spontaneous selective attention: a study of normal twins.** *Psychiatry Res* 1997, **71:**163-74
14. Cannon TD, Huttunen MO, Lonnqvist J, Tuulio-Henriksson A, Pirkola T, Glahn D, Finkelstein J, Hietanen M, Kaprio J, Koskenvuo M: **The inheritance of neuropsychological dysfunction in twins discordant for schizophrenia.** *Am J Hum Genet* 2000, **67:**369-82
15. Pardo PJ, Knesevich MA, Vogler GP, Pardo JV, Towne B, Cloninger CR, Posner MI: **Genetic and state variables of neurocognitive dysfunction in schizophrenia: a twin study.** *Schizophr Bull* 2000, **26:**459-77
16. Goldsmith HH, Lemery KS, Buss KA, Campos JJ: **Genetic analyses of focal aspects of infant temperament.** *Dev Psychol* 1999, **35:**972-85
17. Greenwood PM, Sunderland T, Friz JL, Parasuraman R: **Genetics and visual attention: Selective deficits in healthy adult carriers of the varepsilon 4 allele of the apolipoprotein E gene.** *Proc Natl Acad Sci U S A* 2000, **97:**11661-11666
18. Schmidt LA, Fox NA, Perez-Edgar K, Hu S, Hamer DH: **Association of DRD4 with attention problems in normal childhood development.** *Psychiatr Genet* 2001, **11:**25-9

19. Corbetta M, Kincade JM, Ollinger JM, McAvoy MP, Shulman GL: **Voluntary orienting is dissociated from target detection in human posterior parietal cortex.** *Nat Neurosci* 2000, **3:**292-7
20. Mesulam MM: **A cortical network for directed attention and unilateral neglect.** *Ann Neurol* 1981, **10:**309-25
21. Posner MI, Petersen SE: **The attention system of the human brain.** *Annu Rev Neurosci* 1990, **13:**25-42
22. Posner MI, Fan J: **Attention as an Organ System.** *To appear in Neurobiology of Perception and Communication:From Synapse to Society the IVth De Lange Conference. (Edited by: J Pomerantz) Cambridge UK: Cambridge University Press*
23. Thompson PM, Cannon TD, Narr KL, van Erp T, Poutanen VP, Huttunen M, Lonnqvist J, Standertskjold-Nordenstam CG, Kaprio J, Khaledy M, *et al*: **Genetic influences on brain structure.** *Nat Neurosci* 2001, **4:**1253-8
24. Fan J, McCandliss BD, Sommer T, Raz A, Posner MI: **Testing the efficiency and independence of attentional networks.** *J Cognitive Neurosci* 2001
25. Fan J, Wu Y, Fossella JA, Posner MI: **Assessing the heritability of attentional networks.** *BMC Neurosci* 2001, **2:**14
26. Stanwood GD, Washington RA, Shumsky JS, Levitt P: **Prenatal cocaine exposure produces consistent developmental alterations in dopamine-rich regions of the cerebral cortex.** *Neuroscience* 2001, **106:**5-14
27. McCulloch J, Savaki HE, McCulloch MC, Jehle J, Sokoloff L: **The distribution of alterations in energy metabolism in the rat brain produced by apomorphine.** *Brain Res* 1982, **243:**67-80
28. Geraud G, Arne-Bes MC, Guell A, Bes A: **Reversibility of hemodynamic hypofrontality in schizophrenia.** *J Cereb Blood Flow Metab* 1987, **7:**9-12
29. Witte EA, Marrocco RT: **Alteration of brain noradrenergic activity in rhesus monkeys affects the alerting component of covert orienting.** *Psychopharmacology (Berl)* 1997, **132:**315-23
30. [http://www.ncbi.nlm.nih.gov/LocusLink/LocRpt.cgi?l=1815]
31. Asghari V, Sanyal S, Buchwaldt S, Paterson A, Jovanovic V, Van Tol HH: **Modulation of intracellular cyclic AMP levels by different human dopamine D4 receptor variants.** *J Neurochem* 1995, **65:**1157-65
32. Faraone SV, Doyle AE, Mick E, Biederman J: **Meta-analysis of the association between the 7-repeat allele of the dopamine D(4) receptor gene and attention deficit hyperactivity disorder.** *Am J Psychiatry* 2001, **158:**1052-7
33. Barr CL: **Genetics of childhood disorders: XXII. ADHD, Part 6: The dopamine D4 receptor gene.** *J Am Acad Child Adolesc Psychiatry* 2001, **40:**118-21
34. Okuyama Y, Ishiguro H, Toru M, Arinami T: **A genetic polymorphism in the promoter region of DRD4 associated with expression and schizophrenia.** *Biochem Biophys Res Commun* 1999, **258:**292-5
35. Auerbach JG, Benjamin J, Faroy M, Geller V, Ebstein R: **DRD4 related to infant attention and information processing: a developmental link to ADHD?** *Psychiatr Genet* 2001, **11:**31-5
36. Cruz C, Camarena B, King N, Paez F, Sidenberg D, de la Fuente JR, Nicolini H: **Increased prevalence of the seven-repeat variant of the dopamine D4 receptor gene in patients with obsessive-compulsive disorder with tics.** *Neurosci Lett* 1997, **231:**1-4
37. Comings DE, Gade-Andavolu R, Gonzalez N, Wu S, Muhleman D, Blake H, Dietz G, Saucier G, MacMurray JP: **Comparison of the role of dopamine, serotonin, and noradrenaline genes in ADHD, ODD and conduct disorder: multivariate regression analysis of 20 genes.** *Clin Genet* 2000, **57:**178-96
38. Kaiser R, Konneker M, Henneken M, Dettling M, Muller-Oerlinghausen B, Roots I, Brockmoller J: **Dopamine D4 receptor 48-bp repeat polymorphism: no association with response to antipsychotic treatment, but association with catatonic schizophrenia.** *Mol Psychiatry* 2000, **5:**418-24
39. Paterson AD, Sunohara GA, Kennedy JL: **Dopamine D4 receptor gene: novelty or nonsense?** *Neuropsychopharmacology* 1999, **21:**3-16
40. Ebstein RP, Novick O, Umansky R, Priel B, Osher Y, Blaine D, Bennett ER, Nemanov L, Katz M, Belmaker RH: **Dopamine D4 receptor (D4DR) exon III polymorphism associated with the human personality trait of Novelty Seeking.** *Nat Genet* 1996, **12:**78-80
41. Lakatos K, Nemoda Z, Toth I, Ronai Z, Ney K, Sasvari-Szekely M, Gervai J: **Further evidence for the role of the dopamine D4 receptor (DRD4) gene in attachment disorganization: interaction of the exon III 48-bp repeat and the -521 C/T promoter polymorphisms.** *Mol Psychiatry* 2002, **7:**27-31
42. Benjamin J, Li L, Patterson C, Greenberg BD, Murphy DL, Hamer DH: **Population and familial association between the D4 dopamine receptor gene and measures of Novelty Seeking.** *Nat Genet* 1996, **12:**81-4
43. [http://www.ncbi.nlm.nih.gov/LocusLink/LocRpt.cgi?l=6531]
44. Volkow ND, Wang GJ, Fowler JS, Gatley SJ, Logan J, Ding YS, Hitzemann R, Pappas N: **Dopamine transporter occupancies in the human brain induced by therapeutic doses of oral methylphenidate.** *Am J Psychiatry* 1998, **155:**1325-31
45. Dresel S, Krause J, Krause KH, LaFougere C, Brinkbaumer K, Kung HF, Hahn K, Tatsch K: **Attention deficit hyperactivity disorder: binding of [99mTc]TRODAT-1 to the dopamine transporter before and after methylphenidate treatment.** *Eur J Nucl Med* 2000, **27:**1518-24
46. Mitchell RJ, Howlett S, Earl L, White NG, McComb J, Schanfield MS, Briceno I, Papiha SS, Osipova L, Livshits G, *et al*: **Distribution of the 3' VNTR polymorphism in the human dopamine transporter gene in world populations.** *Hum Biol* 2000, **72:**295-304
47. Jacobsen LK, Staley JK, Zoghbi SS, Seibyl JP, Kosten TR, Innis RB, Gelernter J: **Prediction of dopamine transporter binding availability by genotype: a preliminary report.** *Am J Psychiatry* 2000, **157:**1700-3
48. Cook E: **Molecular Genetic Studies of Attention Deficit Hyperactivity Disorder.** *In: Wenner-Gren Foundations International Symposium: Neurobiology of ADHD; Stockholm.* 2000
49. Greenwood TA, Alexander M, Keck PE, McElroy S, Sadovnick AD, Remick RA, Kelsoe JR: **Evidence for linkage disequilibrium between the dopamine transporter and bipolar disorder.** *Am J Med Genet* 2001, **105:**145-51
50. Ueno S, Nakamura M, Mikami M, Kondoh K, Ishiguro H, Arinami T, Komiyama T, Mitsushio H, Sano A, Tanabe H: **Identification of a novel polymorphism of the human dopamine transporter (DAT1) gene and the significant association with alcoholism.** *Mol Psychiatry* 1999, **4:**552-7
51. Samochowiec J, Rybakowski F, Czerski P, Zakrzewska M, Stepien G, Pelka-Wysiecka J, Horodnicki J, Rybakowski JK, Hauser J: **Polymorphisms in the dopamine, serotonin, and norepinephrine transporter genes and their relationship to temperamental dimensions measured by the Temperament and Character Inventory in healthy volunteers.** *Neuropsychobiology* 2001, **43:**248-53
52. [http://www.ncbi.nlm.nih.gov/LocusLink/LocRpt.cgi?l=1312]
53. Sesack SR, Hawrylak VA, Guido MA, Levey AI: **Cellular and subcellular localization of the dopamine transporter in rat cortex.** *Adv Pharmacol* 1998, **42:**171-4
54. Lachman HM, Morrow B, Shprintzen R, Veit S, Parsia SS, Faedda G, Goldberg R, Kucherlapati R, Papolos DF: **Association of codon 108/158 catechol-O-methyltransferase gene polymorphism with the psychiatric manifestations of velo-cardio-facial syndrome.** *Am J Med Genet* 1996, **67:**468-72
55. Egan MF, Goldberg TE, Kolachana BS, Callicott JH, Mazzanti CM, Straub RE, Goldman D, Weinberger DR: **Effect of COMT Val108/158 Met genotype on frontal lobe function and risk for schizophrenia.** *Proc Natl Acad Sci U S A* 2001, **98:**6917-22
56. Eisenberg J, Mei-Tal G, Steinberg A, Tartakovsky E, Zohar A, Gritsenko I, Nemanov L, Ebstein RP: **Haplotype relative risk study of catechol-O-methyltransferase (COMT) and attention deficit hyperactivity disorder (ADHD): association of the high-enzyme activity Val allele with ADHD impulsive-hyperactive phenotype.** *Am J Med Genet* 1999, **88:**497-502
57. Niehaus DJ, Kinnear CJ, Corfield VA, du Toit PL, van Kradenburg J, Moolman-Smook JC, Weyers JB, Potgieter A, Seedat S, Emsley RA, *et al*: **Association between a catechol-o-methyltransferase polymorphism and obsessive-compulsive disorder in the Afrikaner population.** *J Affect Disord* 2001, **65:**61-5
58. Schindler KM, Richter MA, Kennedy JL, Pato MT, Pato CN: **Association between homozygosity at the COMT gene locus and obsessive compulsive disorder.** *Am J Med Genet* 2000, **96:**721-4
59. Karayiorgou M, Altemus M, Galke BL, Goldman D, Murphy DL, Ott J, Gogos JA: **Genotype determining low catechol-O-methyltransferase activity as a risk factor for obsessive-compulsive disorder.** *Proc Natl Acad Sci U S A* 1997, **94:**4572-5
60. Kinnear C, Niehaus DJ, Seedat S, Moolman-Smook JC, Corfield VA, Malherbe G, Potgieter A, Lombard C, Stein DJ: **Obsessive-compul-**

sive disorder and a novel polymorphism adjacent to the oestrogen response element (ERE 6) upstream from the COMT gene. *Psychiatr Genet* 2001, **11:**85-7
61. Rotondo A, Mazzanti C, L Dell'Osso, Rucci P, Sullivan P, Bouanani S, Gonnelli C, Goldman D, Cassano GB: **Catechol o-methyltransferase, serotonin transporter, and tryptophan hydroxylase gene polymorphisms in bipolar disorder patients with and without comorbid panic disorder.** *Am J Psychiatry* 2002, **159:**23-9
62. Benjamin J, Osher Y, Kotler M, Gritsenko I, Nemanov L, Belmaker RH, Ebstein RP: **Association between tridimensional personality questionnaire (TPQ) traits and three functional polymorphisms: dopamine receptor D4 (DRD4), serotonin transporter promoter region (5-HTTLPR) and catechol O-methyltransferase (COMT).** *Mol Psychiatry* 2000, **5:**96-100
63. [http://www.ncbi.nlm.nih.gov/LocusLink/LocRpt.cgi?l=4128]
64. Zametkin A, Rapoport JL, Murphy DL, Linnoila M, Ismond D: **Treatment of hyperactive children with monoamine oxidase inhibitors. I. Clinical efficacy.** *Arch Gen Psychiatry* 1985, **42:**962-6
65. Brunner NM HG, Breakefield XO, Ropers HH, van Oost BA: **Abnormal behavior associated with a point mutation in the structural gene for monoamine oxidase A.** *Science* 1993, **262:**578-580
66. Caspi A, McClay J, Moffitt TE, Mill J, Martin J, Craig IW, Taylor A, Poulton R: **Role of genotype in the cycle of violence in maltreated children.** *Science* 2002, **297:**851-4
67. Cases O, Seif I, Grimsby J, Gaspar P, Chen K, Pournin S, Muller U, Aguet M, Babinet C, Shih JC, *et al*: **Aggressive behavior and altered amounts of brain serotonin and norepinephrine in mice lacking MAOA.** *Science* 1995, **268:**1763-6
68. Sabol SZ, Hu S, Hamer D: **A functional polymorphism in the monoamine oxidase A gene promoter.** *Hum Genet* 1998, **103:**273-9
69. Payton A, Holmes J, Barrett JH, Hever T, Fitzpatrick H, Trumper AL, Harrington R, McGuffin P, O'Donovan M, Owen M, *et al*: **Examining for association between candidate gene polymorphisms in the dopamine pathway and attention-deficit hyperactivity disorder: a family-based study.** *Am J Med Genet* 2001, **105:**464-70
70. Craddock N, Roberts Q, Williams N, McGuffin P, Owen MJ: **Association study of bipolar disorder using a functional polymorphism (Ser311–>Cys) in the dopamine D2 receptor gene.** *Psychiatr Genet* 1995, **5:**63-5
71. Furlong RA, Ho L, Rubinsztein JS, Walsh C, Paykel ES, Rubinsztein DC: **Analysis of the monoamine oxidase A (MAOA) gene in bipolar affective disorder by association studies, meta-analyses, and sequencing of the promoter.** *Am J Med Genet* 1999, **88:**398-406
72. Lim LC, Powell J, Sham P, Castle D, Hunt N, Murray R, Gill M: **Evidence for a genetic association between alleles of monoamine oxidase A gene and bipolar affective disorder.** *Am J Med Genet* 1995, **60:**325-31
73. Deckert J, Catalano M, Syagailo YV, Bosi M, Okladnova O, Di Bella D, Nothen MM, Maffei P, Franke P, Fritze J, *et al*: **Excess of high activity monoamine oxidase A gene promoter alleles in female patients with panic disorder.** *Hum Mol Genet* 1999, **8:**621-4
74. Samochowiec J, Lesch KP, Rottmann M, Smolka M, Syagailo YV, Okladnova O, Rommelspacher H, Winterer G, Schmidt LG, Sander T: **Association of a regulatory polymorphism in the promoter region of the monoamine oxidase A gene with antisocial alcoholism.** *Psychiatry Res* 1999, **86:**67-72
75. Vanyukov MM, Moss HB, Yu LM, Tarter RE, Deka R: **Preliminary evidence for an association of a dinucleotide repeat polymorphism at the MAOA gene with early onset alcoholism/substance abuse.** *Am J Med Genet* 1995, **60:**122-6
76. Melis A, Soetens E, van der Molen MW: **Process-specific slowing with advancing age: evidence derived from the analysis of sequential effects.** *Brain Cogn* 2002, **49:**420-35
77. Ladosky W, Figueiredo BC, Schneider HT: **Hypothalamic nuclei catechol-O-methyl-transferase and the process of brain sexual differentiation.** *Braz J Med Biol Res* 1984, **17:**107-17
78. Gogos JA, Morgan M, Luine V, Santha M, Ogawa S, Pfaff D, Karayiorgou M: **Catechol-O-methyltransferase-deficient mice exhibit sexually dimorphic changes in catecholamine levels and behavior.** *Proc Natl Acad Sci U S A* 1998, **95:**9991-6
79. Alsobrook JP, Zohar AH 2nd, Leboyer M, Chabane N, Ebstein RP, Pauls DL: **Association between the COMT locus and obsessive-compulsive disorder in females but not males.** *Am J Med Genet* 2002, **114:**116-20
80. Ennis S, Maniatis N, Collins A: **Allelic association and disease mapping.** *Brief Bioinform* 2001, **2:**375-87
81. Swanson J, Oosterlaan J, Murias M, Schuck S, Flodman P, Spence MA, Wasdell M, Ding Y, Chi HC, Smith M, *et al*: **Attention deficit/hyperactivity disorder children with a 7-repeat allele of the dopamine receptor D4 gene have extreme behavior but normal performance on critical neuropsychological tests of attention.** *Proc Natl Acad Sci U S A* 2000, **97:**4754-9
82. Ding YC, Chi HC, Grady DL, Morishima A, Kidd JR, Kidd KK, Flodman P, Spence MA, Schuck S, Swanson JM, *et al*: **Evidence of positive selection acting at the human dopamine receptor D4 gene locus.** *Proc Natl Acad Sci U S A* 2002, **99:**309-14
83. Ladavas E, Nicoletti R, Umilta C, Rizzolatti G: **Right hemisphere interference during negative affect: a reaction time study.** *Neuropsychologia* 1984, **22:**479-85
84. Liotti M, Tucker DM: **Right hemisphere sensitivity to arousal and depression.** *Brain Cogn* 1992, **18:**138-51
85. Luciana M, Collins PF, Depue RA: **Opposing roles for dopamine and serotonin in the modulation of human spatial working memory functions.** *Cereb Cortex* 1998, **8:**218-26
86. Luciana M, Sullivan J, Nelson CA: **Associations between phenylalanine-to-tyrosine ratios and performance on tests of neuropsychological function in adolescents treated early and continuously for phenylketonuria.** *Child Dev* 2001, **72:**1637-52
87. [http://140.251.58.136/~jinfan/ant/ant.html]
88. Lander E, Kruglyak L: **Genetic dissection of complex traits: guidelines for interpreting and reporting linkage results.** *Nat Genet* 1995, **11:**241-7
89. Seaman MI, Fisher JB, Chang F, Kidd KK: **Tandem duplication polymorphism upstream of the dopamine D4 receptor gene (DRD4).** *Am J Med Genet* 1999, **88:**705-9
90. Daly G, Hawi Z, Fitzgerald M, Gill M: **Mapping susceptibility loci in attention deficit hyperactivity disorder: preferential transmission of parental alleles at DAT1, DBH and DRD5 to affected children.** *Mol Psychiatry* 1999, **4:**192-6
91. Daniels JK, Williams NM, Williams J, Jones LA, Cardno AG, Murphy KC, Spurlock G, Riley B, Scambler P, Asherson P, *et al*: **No evidence for allelic association between schizophrenia and a polymorphism determining high or low catechol O-methyltransferase activity.** *Am J Psychiatry* 1996, **153:**268-70
92. Hotamisligil GS, Breakefield XO: **Human monoamine oxidase A gene determines levels of enzyme activity.** *Am J Hum Genet* 1991, **49:**383-92
93. Weir BS: **Genetic Data Analysis II.** *Sinauer Associates, Inc. Sunderland, MA.* 1996

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