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Genes and behavior in preschool children: The relation between dopamine genotype and latent executive control

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Genes and Behavior in Preschool Children:
The Relation between Dopamine Genotype and Latent Executive Control

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Dopamine and Executive Control

➢Dopaminergic neurotransmission is implicated in the executive control of cognition and behavior (Braver & Cohen, 2000)

➢The prefrontal cortex is thought to modulate activity in other brain regions through "bias signals" boosting activation of task-relevant neural pathways, likely through the action of dopamine (Montague, 2004)

➢A number of studies have found associations between executive control and dopamine-related candidate genes, likely because of variation in the availability of dopamine in the synapse and/or efficiency of dopaminergic neurotransmission (Casey, 2002; Roesch-Ely, 2005)

➢Furthermore, dopamine genotype has been found to relate to attention problems and attention deficit/hyperactivity disorder (ADHD; Faraone, 2005)

➢A better understanding of how variation in dopamine genotype relates to children's regulation of attention and behavior has significance for clinical practice and possible intervention

Dopamine Gene Alleles associated with Risk

Gene	Risk Allele
COMT (catechol-O-methyltransferase)	Val allele: associated with higher activity/lower dopamine availability; poorer Wisconsin Card Sorting Test performance (Egan, 2001), increased cortical activation in a working memory task (Bertolino, 2006)
DAT (dopamine transporter)	10-repeat allele: associated with lower caudate volume (Durston, 2005); increased impulsivity in children with ADHD (Kim, 2006), increased cortical activation in a working memory task (Bertolino, 2006)
DRD2 (D2 dopaminergic receptor)	A1 allele: associated with lower receptor availability in striatum; lower inhibitory control (Rodriguez-Jimenez, 2006); increased susceptibility to addiction (Munafo, 2004), and neural response to reward (Cohen, 2005),
DRD4 (D4 dopaminergic receptor)	7-repeat allele: associated with poorer sustained attention (Kieling, 2006), novelty-seeking in males (Laucht, 2006), increased vulnerability to the effects of harsh parenting (Bakermans-Kranenburg, 2006)

Method

➢133 preschool children (mean age 4 years 1 month, range 2.5 to 6 years) were administered an executive control battery that included the following tasks: Delayed Alternation, Continuous Performance Task, DAS Digit Span, Delayed Response, Six Boxes, Shape School, NEPSY Statue, NEPSY Visual Attention, and Tower of Hanoi

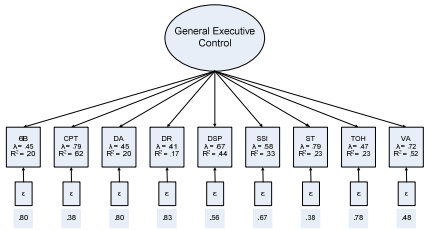
➢Children were genotyped on the COMT, DAT, DRD2, and DRD4 polymorphisms of interest from cheek swabs obtained using a preschooler-friendly "lollipop game" procedure (Espy, 2002)

➢Children were assigned dummy codes of 0 or 1 for each gene, where 1 indicated the presence of the "risk allele"

Latent Executive Control

➢A latent variable approach has been shown to be particularly useful for studying executive control, in that it results in a "purified" measure that capture common variance across executive control tasks that differ in their non-executive demands (Miyake, 2000)

➢Performance on the executive control battery was used to construct a latent variable indexing executive control (Wiebe, Espy, & Charak, under review)



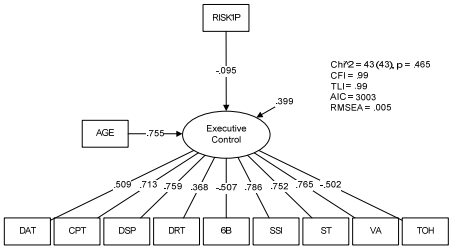
➢Next, the relationship between dopamine genotype and latent and executive control was explored using structural equation modeling, in Mplus Version 4.1 (Muthen, 2006).

Genes and Executive Control: Model 1

➢First, a summary variable was calculated by simply adding up "risk scores" for all dopamine genes of interest

➢This risk score was used to predict latent executive control

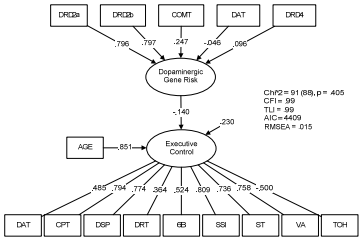
➢Age was also included as a covariate, to account for age differences in executive control



➢While this model demonstrated good fit to the data, the effect of genetic risk did not reach significance (p = .15), although the effect was in the predicted direction (higher genetic risk was related to poorer executive control)

Genes and Executive Control: Model 2

➢To look at the contributions of individual genes, individual dummy variables were used to create a latent Genetic Risk variable, in a Multiple Indicator Multiple Cause (MIMIC) model



➢This model also demonstrated good fit to the data, as evidenced by a non-significant chi-square test

➢However, the effect of genetic risk was statistically significant ($p < .05$)

➢As shown by the loadings of the individual genetic risk dummy variables on the Genetic Risk latent variable

➢The effect can be largely attributed to DRD2 and COMT, as model results do not change substantially when DRD4 and DAT are dropped

Discussion

➢We observed a relationship between dopamine genotype risk score and latent executive control in preschool children:

- ➢Children with alleles of dopaminergic genes that have been previously shown to relate to poorer outcomes had lower values on an Executive Control latent variable.
- ➢This effect seems to be specific to DRD2 and COMT.

➢This study also further demonstrates the utility of a latent variable approach in the study of preschool executive control.

➢These results are consistent with differences in dopamine availability and efficiency of neurotransmission related to different dopamine alleles.

➢Further work is necessary to test this relationship in a larger sample, and to examine the contributions of gene-environment and gene-gene interactions to executive control development

➢Given that executive control problems are implicated in ADHD (Nigg, 2005), these findings may shed light on how genetic risk contributes to behavioral problems.

References

Bakermans-Kranenburg, M. & van Ijzensoorn, M. (2006). Gene-environment interaction of the dopamine D4 receptor (DRD4) and observed maternal insensitivity predicting externalizing behavior in preschoolers. *Developmental Psychobiology, 48*, 406-409.

Bertolino, A., Blasi, G., Latorre, V., Rubino, V., et al. (2006). Additive effects of genetic variation in dopamine regulating genes on working memory cortical activity in human brain. *Journal of Neuroscience, 26*, 3918-3922.

Braver, T., & Cohen, J. (2000). On the control of control: The role of dopamine in regulating prefrontal function and working memory. In S. Monsell & J. Driver (Eds.), *Attention and Performance XVIII; Control of cognitive processes* (pp.713-737).

Casey, B. J., Tottenham, N., & Fossella, J. (2002). Clinical, imaging, lesion, and genetic approaches toward a model of cognitive control. *Developmental Psychobiology, 40*, 237-254.

Cohen, M., Young, J., Baek, J., Kessler, C., & Ranganath, C. (2005). Individual differences in extraversion and dopamine genetics predict neural reward responses. *Brain Research: Cognitive Brain Research, 25*, 851-861.

Egan, M., Goldberg, T., Kolachana, B., Callicott, J., et al. (2001). Effect of COMT Val108/158 Met genotype on frontal lobe function and risk for schizophrenia. *Proceedings of the National Academy of Sciences, 98*, 6917-6922.

Espy, K. A. & Hamby, A. F. (2002). "Getting into the mouths" of preschoolers: A method for obtaining buccal samples for later genotyping. *Developmental Neuropsychology, 21*, 197-200.

Faraone, S. V., Perlis, R. H., Doyle, A. E., Smoller, J. W., et al. (2005). Molecular genetics of attention-deficit/hyperactivity disorder. *Biological Psychiatry, 57*, 1313-1323.

Kieling, C., Roman, T., Doyle, A., Hutz, M., & Rohde, L. (2006). Association between DRD4 gene and performance of children with ADHD in a test of sustained attention. *Biological Psychiatry, 60*, 1163-1165.

Kim, J., Kim, B, & Cho, S. (2006). The dopamine transporter gene and the impulsivity phenotype in attention deficit hyperactivity disorder: A case-control association study in a Korean sample. *Journal of Psychiatric Research, 40*, 730-737.

Laucht, M., Becker, K., & Schmidt, M. (2006). Visual exploratory behaviour in infancy and novelty seeking in adolescence: two developmentally specific phenotypes of DRD4? *Journal of Child Psychology and Psychiatry, 47*, 1143-1151.

Miyake, A., Friedman, N. P., Emerson, M. J., Witzki, A. H., et al. (2000). The unity and diversity of executive functions and their contributions to complex "frontal lobe" tasks: A latent variable analysis. *Cognitive Psychology, 41*, 49-100.

Montague, P. R., Hyman, S. E., & Cohen, J. D. (2004). Computational roles for dopamine in behavioural control. *Nature, 431*, 760-767.

Munafo, M., Clark, T., Johnstone, E., Murphy, M., & Walton, R. (2004). The genetic basis for smoking behavior: A systematic review and meta-analysis. *Nicotine and Tobacco Research, 6*, 583-597.

Muthén, L., & Muthén, B. (2006). *Mplus 4.0 User's Guide*. Los Angeles: Muthén & Muthén.

Nigg, J. T. (2005). Neuropsychologic theory and findings in attention-deficit/hyperactivity disorder: The state of the field and salient challenges for the coming decade. *Biological Psychiatry, 57*, 1424-1435.

Rodriguez-Jiminez, R., Avila, C., Ponce, G., Ibanez, M. I., et al. (2006). The *Taq*IA polymorphism linked to the *DRD2* gene is related to lower attention and less inhibitory control in alcoholic patients. *European Psychiatry, 21*, 66-69.

Roesch-Ely, D., Scheffel, H., Weiland, S., Schwaninger, M., et al. (2005). Differential dopaminergic modulation of executive control in healthy subjects. *Psychopharmacology, 178*, 420-430.

Wiebe, S., Charak, D., & Espy, K. (under review). *Using confirmatory factor analysis to understand executive control in preschool children: I. Latent structure.* Manuscript submitted for publication.

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