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# Genetic factors in preschool executive control: Relations between serotonin genotype, working memory, and set shifting

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# Genetic factors in preschool executive control: Relations between serotonin genotype, working memory, and set shifting

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## Executive Control in Preschool Children

➢ Executive control includes a number of higher cognitive abilities important for goal-directed behavior, including working memory, inhibitory control, and set shifting/cognitive flexibility (Miyake et al., 2000).
➢Executive control undergoes protracted development through childhood and adolescence, in parallel with frontal structures that are thought to underlie this development.
➢The preschool years are an important phase in development of these skills.

## Serotonin and Executive Control

➢Serotonin is thought to play a regulatory role in cognitive processes.
➢Serotonergic (5-HT) neurons project from the raphe nuclei to regions throughout the cortex, with extensive projections to frontal regions including orbitofrontal cortex (OFC) and dorsolateral prefrontal cortex (DLPFC; Gingrich & Hen, 2001).
➢The serotonin transporter (5-HTT) plays a key role in clearing 5-HT from the synapse, and is the target for selective serotonin reuptake inhibitors (SSRIs).
➢There is a common insertion/deletion polymorphism in the promoter region for the serotonin transporter gene.
➢This gene has a short and a long allele that differ functionally: the long allele is more transcriptionally active (i.e., more protein is manufactured, resulting in greater efficiency in 5-HT reuptake; Hariri et al., 2002)
➢Candidate gene studies examine the relation between the genotype of specific proteins involved in neural function and individual differences in behavior (e.g., Casey et al., 2002).
➢Serotonin is best known for its involvement in emotion related processing: 5-HTTLPR genotype has been shown to relate to individual differences in processing of emotional stimuli (Hariri et al., 2002) and vulnerability to depression in the face of negative life events (Caspi et al., 2002).
➢Individuals with attention deficit/hyperactivity disorder are more likely to carry the short allele of the transporter gene (Kent et al., 2002).
➢Some have argued that low serotonin is related to impulsivity and inhibitory control, particularly in clinical populations (e.g., Evenden, 1999); however, empirical findings related to response inhibition have been inconsistent in normal adults (Clark et al., 2005).
➢In non-human primates, reducing serotonin in OFC results in difficulties in learning a detour-reaching inhibitory control task (Walker et al., 2006), and in impairments in reversal learning (Clarke et al., 2005).
➢Luciana et al.(2001) found that increasing serotonin levels in normal adults by loading tryptophan (the precursor to 5-HT) resulted in impairments in spatial working memory and memory for affective stimuli.
➢In the present study, we explored the relation between serotonin genotype and children's executive control in the preschool years.

## Method

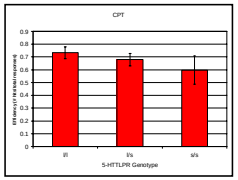
➢A sample of 166 children between ages of 2.5 and 6 years completed battery of executive control tasks including several measures of inhibitory control (NEPSY Statue, Whisper, Preschool Continuous Performance task), working memory (Delayed Alternation, Digit Span, 6 Boxes-Spatial Version) and set shifting (Spatial Reversal); across tasks, the number of children whose data could be included in analyses ranged from 109 to 165.
➢Cheek swabs were obtained using a preschooler-friendly "lollipop game" (Espy & Hamby, 2002).
➢Children were genotyped on 5-HTTLPR, and classified as s/s, s/l, or l/l (0, 1, or 2 copies of the high-risk long allele).
➢Allele frequencies are similar to those reported in other studies examining 5-HTTLPR and frequencies for each polymorphism did not differ from those expected under Hardy-Weinberg equilibrium ($\chi 2 = 0.01$, $p > .90$).
➢Demographic information for the 3 genotype groups is presented in the table

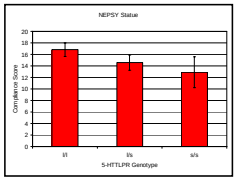
| | 5-HTTLPR Genotype | | |
|---|---|---|---|
| | l/l | l/s | s/s |
| Sex | 31 girls, 34 boys | 42 girls, 36 boys | 13 girls, 10 boys |
| Age | 3.75 | 3.59 | 3.78 |
| Maternal Education (years) | 14.17 | 14.27 | 13.76 |

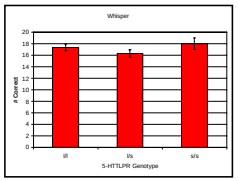
➢All analyses included age as a covariate to control for developmental differences in performance.

## Results: Inhibitory Control

➢Inhibition tasks did not differ by serotonin genotype (all *ps* > .22).

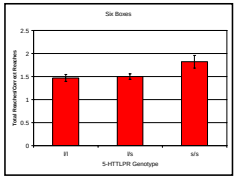


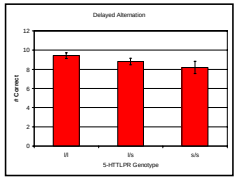



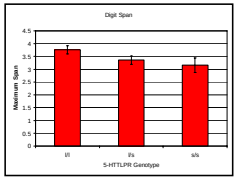

## Results: Working Memory

➢There was a significant effect of genotype for 6 Boxes, $F(2, 158) = 4.35$, $p < .02$.
➢The s/s genotype was associated with poor performance that differed significantly from the s/l and l/l genotypes.



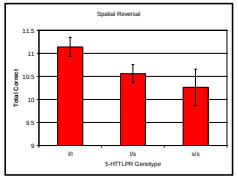

➢Similar trends were observed for delayed alternation and digit span, but the main effect of genotype was not statistically significant for either task when age was controlled, ps < .15.




## Results: Set Shifting

➢For spatial reversal, there was a significant effect of genotype, $F(2, 161) = 3.01$, $p = .05$.
➢Both groups of children who had a copy of the short allele evidenced poorer performance than children who did not.




## Discussion

➢These findings support a connection between serotonin genotype and executive control in preschool children, but the pattern of results differ depending on the particular cognitive function under consideration.
➢In general, the short allele of the serotonin transporter promoter gene is associated with poorer outcomes on tasks, although for many tasks the differences did not reach statistical significance.
➢In part this may be attributable to the small size of the s/s group (representative of the frequency of this genotype in the population)
➢For working memory, it appeared that the presence of one or more copies of the long allele (better reuptake, less 5-HT in synapse) was protective, and associated with better performance.
➢Children with one or two copies of the short allele (more 5-HT in synapse) evidenced poorer performance on set shifting.
➢The set-shifting results are at odds with animal research linking inflexible responding to reduced 5-HT.
➢However, effects of acute loading/deprivation effects sometimes differ from effects of neurotransmitter differences present across development (Ansorge et al., 2004).
➢Serotonin genotype did not relate to inhibitory control, perhaps because the tasks we used to measure this construct did not have a strong emotional or motivational component.
➢Further work is necessary to test for replication of these findings.
➢Future work should include a larger sample, to increase power related to the less frequent, high-risk s/s group.
➢It will be critical to assess potential interactions with the environment (e.g., stressful life events, parenting) and with other genes (e.g., genes involved in dopaminergic neurotransmission).

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