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Research article

A Polymorphism Related to Methylation Influences Attention during Performance of Speeded Skills

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Abstract: The executive attention network is important for resolving conflict among responses thus allowing us to control voluntary behavior in the face of competition. We have previously shown that individual differences in the efficiency of performing conflict tasks are related to genetic differences. In this study we examine whether performance by adults in conflict tasks is related to a polymorphism that influences the efficiency of methylation. We find that variation in a gene associated with higher rates of methylation is related to better performance in speeded tasks involving the resolution of conflict. Reaction time in conflict tasks improves with development and with practice. Although most theories of skilled performance support a monotonic improvement in reaction time with practice, our data suggest that for some people, waning attention can lead to an increase in reaction time late in practice. Variation in a gene facilitating norepinephrine production was associated with increased reaction time. We discuss the efficiency of myelination and release of dopamine within neural networks relevant to the resolution of conflict as possible mechanisms for methylation as an influence on skilled behavior.

Key words: attention networks; epigenetics; genes; methylation; myelination; skill learning

Abbreviations: catechol *O*-methyltransferase (COMT); dopamine β-hydroxylase (DBH); methylenetetrahydrofolate reductase (MTHFR); Attention Network Test (ANT); National Center for Biotech Information (NCBI); Reaction time (RT); **A** = adenosine, **C** = cytidine , **G** = guanosine, **T** = thymidine

1. Introduction

The executive attention network is important for resolving conflict among competing responses [1]. A major part of that network is the anterior cingulate gyrus, modulated by dopamine from the ventral tegmental area. Genetic variations that influence dopamine have been shown to relate to the time to resolve conflict [2,3]. For example, the G158A genetic variation of catechol *O*-methyltransferase (COMT) gene, whose product metabolizes dopamine, has been related to individual differences in conflict related tasks [4]. Electrophysiological markers of conflict resolution are also related to allelic variations of COMT [5].

Genes related to norepinephrine are involved in the ability to obtain and maintain alertness [2,3]. Alertness during sustained attention tasks has been related to variation in the gene dopamine β-hydroxylase (DBH), whose product converts dopamine to norepinephrine. In a timed attention task, DBH was associated with individual differences in the number of errors, and with differences in reaction time [6]. In our child study [7], children with the 444G polymorphism of DBH showed a strong upswing in RT between days 2 and 3 of practice, suggesting that RT increases were related to a reduced level of alerting with sustained practice.

While genetic variation can change gene expression resulting in behavioral effects, a growing body of research has demonstrated that epigenetic modification of genes such as methylation also influences gene expression and behavior. Epigenetic regulation of gene expression has been associated with environmental influence and learning. In an associative learning task performed by rats, gene methylation was required for new learning to occur and these changes were dependent on neural activity [8]. Gene methylation requires functioning of the folate metabolic pathway, and the gene encoding methylenetetrahydrofolate reductase (MTHFR) facilitates the production of a methyl precursor used in methylation reactions. Variation in the MTHFR gene has been associated with attention deficits and processing speed in child leukemia survivors [9] and cognitive ability in elderly males [10]. An association between genetic variation in MTHFR and COMT predicted the number of errors in a task requiring executive function in schizophrenia patients [11]. Methylation thus relates to performance in cognitive tasks.

In our previous work [7] we found that 7 year old children homozygous for the 677C allele of the MTHFR gene, associated with superior methylation, and the 158A (Met) allele of COMT, known to influence executive attention, showed greater improvement in overall reaction time and resolution of conflict when performing the Attention Network Test (ANT). To determine the generality of our previous observations of learning in children, we have trained undergraduate students in several learning tasks, two of which measure reaction time and a third task is unspeeded. We ask if polymorphisms in a gene related to methylation efficiency (MTHFR) alone or in conjunction with one relating to attention (COMT), influence performance on the ANT in adults as we have found for children [7]. We also ask if a gene related to sustaining attention (DBH) is involved in increases in RT during practice. Finally, we examined the relation of these genes to explicit and implicit

performance of skills that involve speed of response and to an unspeeded paired associate learning task.

2. Materials and Methods

Seventy undergraduate students at the University of Oregon (26 Male) volunteered to participate in three one hour sessions over a two week period. They were paid $15 per hour. Each day the students performed each of the three tasks described below. Written consent was obtained in the first session for participation in the study, and procedures were approved by the Institutional Review Board of the University of Oregon.

2.1. Behavioral tasks

2.1.1. Attention network test (ANT)

To examine the alerting, orienting and conflict resolution networks of attention, 70 participants performed the ANT [12] three times, once in each session. The ANT requires participants to press a key in the direction of a target arrow surrounded by flanker arrows [13] which can be congruent (point in the same direction), or incongruent (point in the opposite direction) with the target. The response time averaged over all conditions we call the overall reaction time (RT). The difference between incongruent and congruent trials has been shown to correlate with activation of the dorsal anterior cingulate and is thought to be a measure of the ability to resolve conflict [14]. We use the term conflict scores for this subtraction. Cues introduced before the target inform participants of where and when the target will occur, allowing measures of the orienting and alerting network. Participants were given 128 trials in each of the three sessions and reaction time and error rates were recorded.

In our previous study the child version of the ANT was used. The difference between the adult version and the child ANT must be taken into consideration when viewing Figure 1. The adult version uses arrows as the target and the child version uses animals, so children follow a story that requires them to press the key in the direction that the center animal is moving. Three sets of 32 targets were used in each of the three sessions, half of the target animals pointed left and half right, flankers were either pointing in the same (congruent) or opposite (incongruent) direction as the target. Prior to the target different cue conditions were presented to measure the alerting and orienting network. The child pressed one of two buttons to designate the direction in which the target animal's head pointed, RT and errors were recorded.

2.1.2. Serial reaction time task

All 70 subjects performed the serial task in each session, measuring both explicit learning and implicit performance through reaction time and accuracy. Following the Curran and Keele [15] method and using computer graphics, a sequence of targets were presented in an arrangement of four locations on the screen. When an 'X' is presented, the participant is to press the key under that location as rapidly as possible. Performance on trials with a repeating fixed sequence is compared with trials in which the sequence is random to yield the explicit learning measure. Increased speed with repeated trials is a measure of learning of the sequence. By use of a divided attention task, explicit efforts to identify and perform the previously learned sequence are reduced and there is a relatively pure implicit performance measure. 12 blocks of 120 trials are presented, beginning with two practice blocks of the dual (divided attention) task using random trials and three practice blocks of the single task using a fixed sequence. Both the implicit and explicit measures are preceded by at least one practice block and the experimental measures are performed in sequence. A different fixed sequence of six stimuli is presented in each session. Subjects are not informed as to the presence or absence of a fixed sequence.

2.1.3. Paired associates test

All 70 subjects performed the paired associates test in each session or until all word pairs were remembered correctly. This task measures word association learning. Using computer graphics, during a viewing phase 30 word pairs are shown sequentially, followed by a testing phase. In the testing phase stimulus words are randomly displayed for 2 seconds, during this interval the person generates a spoken response by naming its paired word. After the response interval, stimulus and response words are shown together for 2 seconds, providing another opportunity to learn the association. Subjects are instructed to try to name the word prior to the response appearing. One viewing block and three testing blocks were presented in each session unless the participant was correct on all pairs, thus completing the task. The percent correct for the 30 pairs are measured on each replication and number of trials to completion is scored.

2.2. Genetic analysis

All subjects submitted saliva samples for analysis during session 1. The relative allele frequencies for each gene were not significantly different than expected based on global frequencies (NCBI). The allelic frequencies for the genotype groupings are shown in Table 1.

The demographic distribution was as follows: 39 caucasian, 15 asian, 1 pacific islander, 1 african american, 4 selected 'other' ethnicity, and 12 did not specify ethnicity. Four of the subjects identified with a hispanic heritage.

Table 1. Number of participants for gene X gene interaction in adults.

	COMT		DBH	
	AA	GA/GG	GG	AG/AA
MTHFR				
CC	7	32	8	31
TC/TT	4	27	3	28

Saliva samples were collected using Oragene collection tubes (DNA Genotek) and processed according to the suggested DNA extraction protocol. The COMT genotype at rs4680 (Val108/158Met) was assayed according to the method of Daniels et al [16], and the reaction conditions are described in our previous work [17]. The DBH rs1108580 (G444A) variation was amplified using oligonucleotides from Cubells et al [18] and the following conditions: 200μM each dNTP, 3 mM $MgCl_2$, 1× $(NH4)_2SO_4$ buffer, 2.5 units recombinant Taq polymerase (Fermentas), and 20 ng DNA. The amplification proceeded at 94°C for 3 min, then cycled 40 times at 94°C 30 sec, 60°C 30 sec and 72°C 30 sec, followed by 3 min at 72°C. The products were digested with EcoNI at 37° and resolved in 3% high resolution agarose. The MTHFR rs1801133 variation was assayed using the following primers: forward 5'-CGAAGCAGGGAGCTTTGAGG-3' and reverse 5'-AGGACGGTGCGGTGAGAGTG-3'. The reaction conditions were similar to that of DBH, with the following differences: 1.5 mM $MgCl_2$, and an annealing temperature of 56°C. Fragments were digested at 37°C with HinfI and the 233 bp (C allele)/176 bp (T allele) products resolved in 2.5% agarose.

2.3. Statistical analysis

We divided MTHFR, COMT, and DBH into allelic groups shown in Table 1. For each task we used ANOVA to determine significant effects on RT and/or errors of allelic groups as a function of practice (sessions or blocks). In the case of implicit and explicit learning measures and speed measures we calculated product moment correlations between scores.

3. Results

3.1. ANT behavioral effects

We first compare our overall ANT reaction time between children in our previous work [7], and adults, in the current study. We found an average improvement in overall RT of about 400 millisec between age 7 children and adults (See Figure 1). The version of the flanker task was different for 7 year olds than adults. These differences (see method section) made the child version somewhat easier

and the RT differences between the two ages may be less than they would otherwise be. It should be noted that in a recent large scale study using the arrow version of the flanker task at all ages [19], at age 7 overall RT was about 1100 msec and for adults it was about 640 msec; a difference of 460 msec. This result is quite similar to what we found. In that study [19] conflict scores were about 130 msec at age 7 and about 70 msec for adults. The average conflict score in our adult study was also 70 msec (see Figure 3A and B). Since in our child study [7], the conflict was introduced by the animals rather than arrows, conflict scores are not comparable at the two ages.

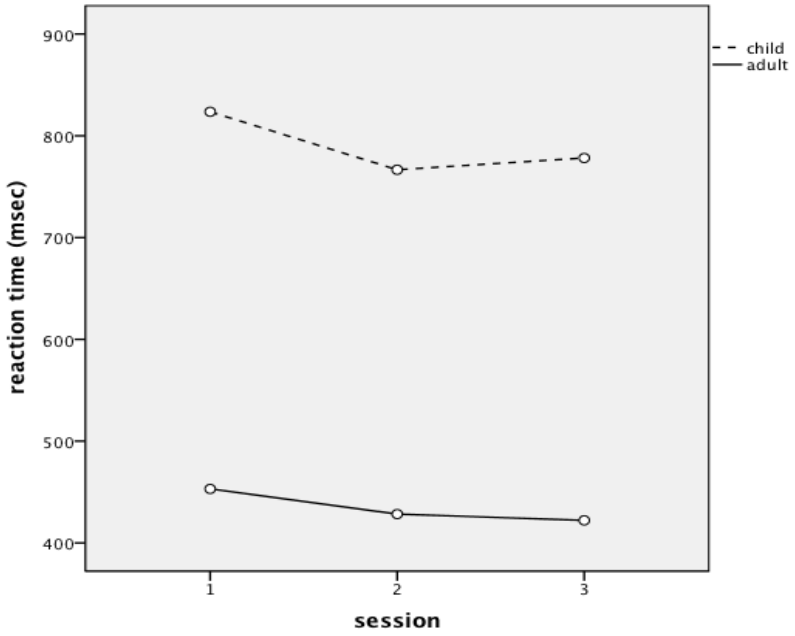

Figure 1. Comparison of 7 year old children and adults in ANT Reaction Times.

We also observed practice effects over three sessions (see method) and found improved RT over the three sessions at both ages of about 40 millisec. Both the faster RTs for adults ($F(1,412) = 1518$, $p < 0.001$) and the improvement with practice for both groups ($F(2,412) = 7.5$, $p < 0.001$) are significant. There is no interaction between the two ($F(2,412) = 1.9$, $p > 0.05$). The reduced RT with age is about 10 times as large as the improvement with training at a given age. Only the child data shows a mean upswing between session 2 and 3, which is not significant overall, but is significant for children homozygous for the G allele of the DBH gene.

3.2. Other behavioral tasks

In our previous study with children, we measured learning using the ANT and a behavioral task similar to the game Simon Says [7]. In this study we looked at learning in adults using the ANT, a serial reaction time task that allowed separate estimates of explicit learning and implicit performance,

and an unspeeded verbal learning task. Figure 2 shows the mean RT for all participants during each block of the serial reaction time task. The unshaded region contains blocks in which an auditory task was performed at the same time as the serial reaction time task. The shaded block shows where the serial reaction time task was run alone. Triangular symbols represent trials with a fixed sequence and circular symbols represent random trials.

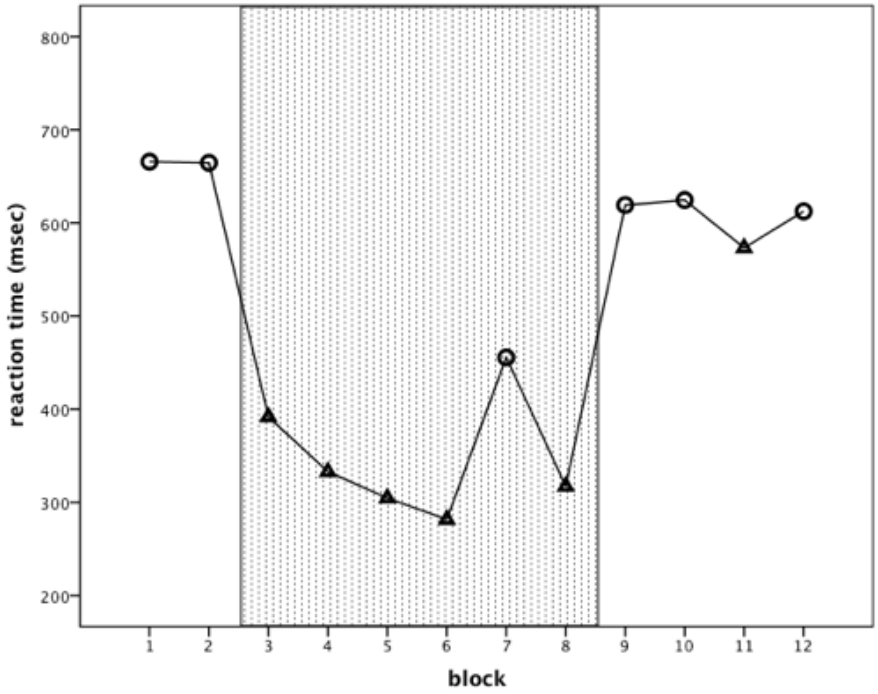

Figure 2. Mean RT for different blocks of the serial reaction time task.

There are two measures of explicit learning, both from blocks where only a single task is performed. The first explicit learning measure is the change in RT between block 3 and 6 (see Figure 2) during repeated practice of a fixed sequence. The second is the difference in RT between block 8 and the average of blocks 7 and 9. This subtraction measures performance after learning of the fixed sequence (block 3–6) in comparison with random trials (block 8). These blocks all take place during the single task phase and reflect specific learning of the sequence rather than general learning of how to carry out the task. We found a high correlation (r = 0.69) between two measures of explicit learning in the serial reaction time task. We found no correlation between explicit learning as measured by either of the methods described above and implicit performance as measured by the difference between ordered (block 11) and random (blocks 10 and 12, averaged) trials, all measured during the dual task condition. There was also a significant correlation between overall RT in the ANT and block 7 of the serial learning task, which most resembles ANT trials with single task random sequences (e.g. Day 1 r = 0.66, $p < 0.001$), suggesting a general tendency to be fast or slow regardless of the task.

3.3. Genetic & epigenetic effects

Previously we reported that the extent of improvement found in the ANT with repeated trials in children depended in part upon the efficiency of methylation, one form of epigenetic effect [7]. Of course adults, like children, differ widely in their ability to resolve conflict and in their improvement with practice. In this paper we seek to determine the possible role of methylation on the ability to resolve conflict in the ANT and also in other cognitive tasks.

In the child data we found a significant effect of allelic variation in MTHFR in interaction with that of COMT on learning and performance. This was true for both overall RT and for conflict. For the MTHFR gene, children with the CC genotype showed a stronger improvement over the three days, but carriers of the T allele showed better overall performance in both reaction time and the resolution of conflict.

COMT has been shown to influence executive attention through its association with conflict [4], Figure 3 shows adult conflict scores in the ANT for combinations of alleles of MTHFR and COMT. There is a main effect of the MTHFR variation on conflict ($F(2,132) = 5.55$, $p = 0.005$). There is also a significant interaction between COMT and MTHFR alleles on conflict ($F(2,132) = 3.11$, $p = 0.048$). The graph shows clearly that performance associated with MTHFR differs only in COMT individuals homozygous for the A allele. This is similar to what was found for children. The adult results differ from the child results in that for adults the CC genotype is associated with generally smaller conflict scores than T carriers, but the T carriers show a greater reduction in conflict scores with practice. Our adult findings are in line with other literature with adults which has shown the disadvantage of the T allele for task performance. One possible reason for this difference with age would be that it reflects that the task (pressing a key as to whether an arrow points right or left) is less novel for adults and requires relatively little learning, while the conflict task is more novel for children so that learning is more critical for them. The main effect of MTHFR on conflict is based on an N greater than 30 in each cell, but as shown in Table 1 the interaction is based on very lows Ns in some cells. Therefore it is important to point out that although the main effect is clear, the status of the interaction between COMT and MTHFR is less clear.

3.3.1. Reduced attention

Unlike the children, mean RT in adults continues to improve from day 2 to day 3, although very slightly. Nonetheless there is some evidence that DBH influences the scores from Day 2 to Day 3. Although there is no main effect of DBH on these RTs there is a trend toward an interaction between DBH and MTHFR on improvement in RT between these two days ($F(1,66) = 3.82$, $p = 0.055$). Only individuals homozygous for the GG genotype of DBH, associated with poorer attentional performance in children, who are carriers of the less efficient methylation T allele of MTHFR show an upswing in RT from day 2 to day 3. There is a similar effect for the mean RT of block 7 in the

serial experiment, which is most analogous to the ANT with single task random trials. The trajectory of RT improvement is slower for individuals with the low attention genotype and less efficient methylation allele (F (2,132) = 3.86, p = 0.024). Unfortunately, the cell sizes are low for the DBH GG groups as shown in Table 1.

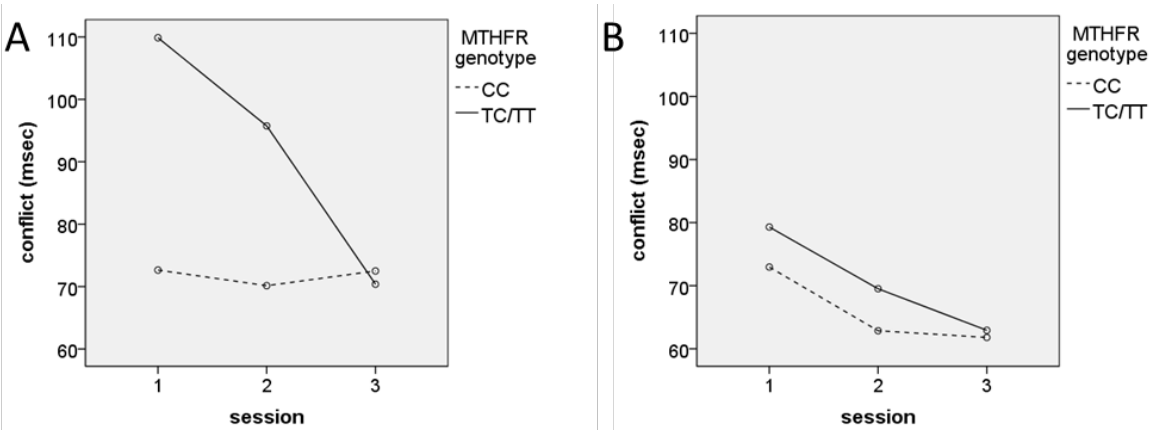

Figure 3. Conflict RTs in the ANT (incongruent flanker RT-congruent flanker RT) for each day of training. These conflict results are shown in panel A for the two allelic groups of MTHFR together with the COMT AA allele. Panel B shows the same two MTHFR groups with the COMT AG/GG genotypes.

3.3.2. Explicit learning

There was no significant overall effect of MTHFR alleles on explicit learning. However, between Days 2 and 3 individuals with the MTHFR CC genotype had an improvement in explicit learning scores while for MTHFR T carriers explicit learning scores declined (F (1,66) = 4.61, p = 0.035).

As shown in Figure 4, the CC group of MTHFR when combined with COMT AA had marginally higher explicit learning scores over the 3 days (F (1,66) = 3.85, p = 0.054). There was no difference for the G present COMT group. This was the same interaction found for the ANT in adults and children. Taking the mean explicit score on days 2, and 3 there is a main effect of MTHFR (F (1,66) = 4.29, p = 0.042) and an interaction between MTHFR and COMT (F (1,66) =4.61, p = 0.035).

We also found slower performance of the repeated pattern (blocks 3–6) in each session by the MTHFR T carriers with the COMT AA genotype. Although this did not reach significance, the slope of improvement is lower than all the other groups.

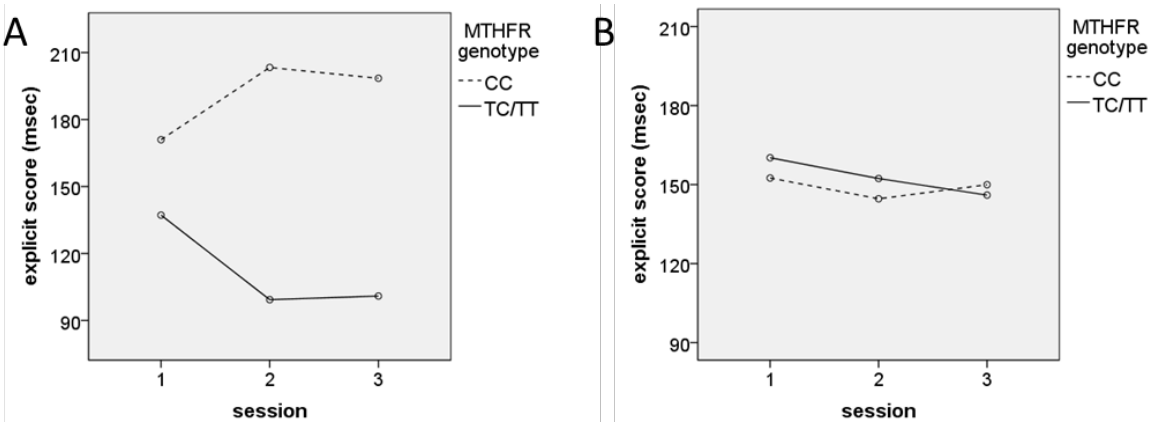

Figure 4. Explicit learning scores (RT for block 7 - RT for mean of block 6 and 8) for each day of the serial RT task as a function of MTHFR genotype and (A) COMT AA or (B) COMT AG/GG genotype.

3.3.3. Implicit performance

There is a significant main effect of MTHFR for implicit performance over the three days with carriers of the MTHFR T allele showing a decline in performance over the sessions (F (2,136) = 3.44, p = 0.035), while CC individuals performed at consistently high levels.

Figure 5 shows the RT for each block of the serial RT test for each day. There was a significant improvement over the three days in RT in the dual task condition for those homozygous for the MTHFR C allele and COMT A allele. This shows for implicit scores the same trend shown for explicit scores in Figure 4 Panel A. For random trials, these individuals performed most poorly in the first session, but improved the most over the sessions (F (2,130) = 4.90, p = 0.009). Carriers of the COMT G allele did not show a difference in performance by MTHFR genotype. This agrees with the finding for explicit scores shown in Figure 4.

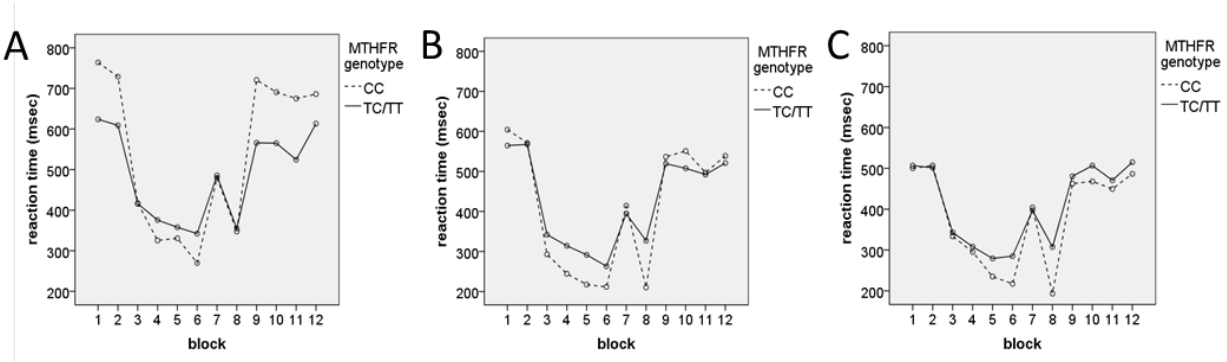

Figure 5. Overall RT for all blocks of the Serial RT task by MTHFR variation with the AA group of COMT (A) Day 1, (B) Day 2, and (C) Day3.

3.3.4. Paired associate learning

The mean scores of percent correct trials by block followed a logarithmic function, where learning was initially rapid, then slowed. The paired associate learning task did not show significant effects for any of the allelic groups studied, either for number of trials to completion or for the slope of percent correct trials by block.

4. Discussion

There appear to be substantial effects of both practice and age on the overall speed of responding. Both children and adults improve in performance with practice (See Figure 1). Exact comparisons are difficult because the children used the child version of the ANT, while adults used the adult version. However, the child version generally results in faster RTs than the adult version, so the differences due to age might be even greater if the adult version had been used for both. Moreover, other studies also show a clear consistent improvement in overall RT with age from age 4 to adults [19,20]. There is somewhat less clarity about the effect of age on the resolution of conflict. One study shows improvement from age 6 to 8 and no change after age 8 [20]. A more recent and larger study shows improvement in conflict score from age 4 to teen age and little change after that [19]. The two studies have many differences, but both show that with development, at least during childhood, there is improvement in the ability to resolve conflict.

There is substantial evidence that improved RT with age is related to the myelination of large fiber tracts [19]. Despite the greater change in RT with age than with practice we believe it is possible that the two effects are due to similar mechanisms. The significant effects of the MTHFR gene, most often in interaction with COMT, on the conflict network of the ANT and on learning in the serial reaction time task, suggest that efficient methylation is an important determinant of RT with practice at both ages. One effect of methylation is to improve myelination [21]. Many studies of mice and humans have shown that learning of various sorts can improve myelination [22,23]. Thus one way in which both development and practice could provide a means of improving reaction time is through improved speed and reliability of performance due to myelination of fibers connecting brain areas related to the task. Although changes in myelin due to learning may be slight, particularly in adulthood, these changes may help synchronize activity in remote brain areas active during the task [23].

Our results with the adult ANT mainly show that the CC genotype of MTHFR gave superior performance in reaction time when combined with COMT AA. However, for the children, CC combined with AA showed worse performance on Day 1 and 2 but a much stronger overall learning effect [7]. The child result was surprising because substantial adult work had shown better overall performance with the MTHFR CC genotype [11,24]. We speculate that the Attention Network Test was rather novel for children, but for adults responding in the direction of an arrow was quite

routinely. Perhaps if superior learning occurs for novel tasks in childhood among individuals homozygous for alleles related to efficient methylation and better executive function, in adults the difference might be in the direction of better performance since most of the learning has already taken place. The serial task with its repeating sequence showed better explicit learning for MTHFR CC individuals with COMT AA, and this group also showed better performance in the random dual task trials over the 3 sessions, so there is support for improved learning with more efficient methylation in adults as well as for children.

Although we found significant effects of alleles that modulated the efficiency of methylation on learning and/or performance in children and adults in the ANT and serial learning tasks, no differences were found in our verbal learning task. We believe this suggests that differences in myelination provide better learning and/or performance in speeded tasks, but this effect may not apply to tasks like verbal learning in which speed was not important. Future human studies should keep this task distinction in mind in examining behavioral tasks. We also observed that MTHFR was associated with both explicit and implicit speeded tasks, supporting a common mechanism in learning.

Many studies of human skilled performance show that a power function relates the number of trials of practice to the reaction time to perform the skill [25–27], although it is possible that exponential functions can sometimes fit better [28]. Regardless of the exact shape of the function, most general theories identify a single underlying process such as improved chunking or more efficient subroutines to account for the learning curve [25,27]. A major finding of our study is the separation between improvement of performance and later increases in RT. Although there was no overall upswing in RT from Day 2 to 3 in the adult study, an upswing was found for adults with the combination of alleles related to poorer methylation (T allele of MTHFR) and low attention (GG genotype of DBH). With children a similar increase in RT between Day 2 and 3 was found for the GG genotype of DBH. Many human skills show a monotonic decrease in RT with practice (25–28). Our averaged results for adults did show a monotonic decrease in RT, but specific child and adult groups showed upswings from day 2 to day 3, which is inconsistent with any monotonic function. We believe that waning attention accounted for these results since DBH, a gene associated with sustained attention [6], was involved in the upswing. In general, children show this increased reaction time much more strongly than adults. Older behavioral learning theories [29] based primarily on rat studies have suggested that each trial produces both improvements due to practice and inhibition due to fatigue. Our results fit more with practice contributing to both faster RT, possibly due to improved connectivity, and slower RT over time due to waning alertness. The effect of DBH was limited to explicit learning, as would be predicted by the role of DBH in maintaining an alert state of attention. Cellular studies in rodents [30] show that maintaining alertness depends on pathways from the locus ceruleus to the anterior cingulate, allowing executive attention to aid in the maintenance of attention.

As pointed out earlier [21] improved myelin might occur through epigenetic factors in which methylation changes gene expression. It has also been observed that methylation of the myelin basic protein at Arg107 improves its function mediating the formation and stability of the myelin sheath [31]. An alternate hypothesis to an effect on gene expression is that methylation works through activation of the dopamine D4 receptor (DRD4). Activity of the D4 receptor is known to influence the ability to resolve conflict in children [32] and adults [33]. Dopamine-dependent activation of DRD4 stimulates phospholipid methylation of the membrane surrounding the receptor using 5-methyltetrahydrofolate, a metabolite of the folate cycle, as methyl donor [34]. Phospholipid methylation alters the fluidity of the membrane, this is believed to alter the structure and function of local ion channels which may impact neural synchrony. Kuznetsova and Deth [35] hypothesized that these changes related to the neural oscillatory transition from beta to gamma, as seen during attention. Decreased MTHFR activity could interfere with changes in neural synchrony by limiting the availability of 5-methyltetrahydrofolate.

In summary, we have found that an allele of MTHFR that provides better methylation significantly improves either learning in child studies and performance in adult studies. One possibility is that these effects are due to improved myelination causing faster conduction between the remote brain areas found to be involved in most cognitive tasks. Another possibility is that MTHFR is working to vary the availability of dopamine. There also may be other mechanisms by which MTHFR works. Our current methods do not allow determination of these mechanisms nor allow us to determine if MTHFR works via a different mechanism than modulation of the genome, or that a correlated genetic influence might be responsible for these effects. Future animal studies may be able to show more directly the genetic and epigenetic mechanism that influence reaction time over development and in skill learning.

Acknowledgments

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Conflict of Interest

All authors declare no conflicts of interest in this paper.

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