The *SNAP25* Gene Is Linked to Working Memory Capacity and Maturation of the Posterior Cingulate Cortex During Childhood

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Background: Working memory (WM) is the ability to retain task relevant information. This ability is important for a wide range of cognitive tasks, and WM deficits are a central cognitive impairment in neurodevelopment disorders such as attention-deficit/hyperactivity disorder (ADHD). Although WM capacity is known to be highly heritable, most genes involved remain unidentified.

Methods: Single nucleotide polymorphisms in genes previously associated with cognitive functions or ADHD were selected for genotyping. Associations of these with WM tasks were investigated in a community sample of 330 children and young adults. One single nucleotide polymorphisms was also investigated in an independent sample of 88 4-year-old children. Furthermore, association between brain structure and activity, as measured by magnetic resonance imaging techniques, and single nucleotide polymorphisms alleles were estimated in 88 participants.

Results: Genotype at rs363039, located in the gene coding for synaptosomal-associated protein, 25 kDa (*SNAP25*) was associated to WM capacity in both samples. Associations in the community sample were also found with measures of other cognitive functions. In addition, this polymorphism affected the gray matter and brain activity in the posterior cingulate cortex, an area included in the so-called default mode network previously correlated to regulation of attention and hypothesized to be implicated in ADHD.

Conclusions: A novel gene–brain–behavior network was identified in which a genotype located in *SNAP25* affects WM and has age-dependent effects on both brain structure and brain activity. Identifying such networks could be a key to better understanding cognitive development as well as some of its disorders.

Key Words: Child development, cognitive development, default network, genetics, posterior cingulate cortex, working memory

A gradual increase in working memory (WM) capacity during childhood is crucial for the development of general intellectual ability and academic performance (1–3). Clinically, a deficit in WM capacity is considered a central cognitive impairment in several neurodevelopment disorders such as attention-deficit/hyperactivity disorder (ADHD) (4,5) and schizophrenia (6). Twin studies have estimated WM capacity to have a strong genetic component (7,8), but few specific genes contributing to this heritability have been identified.

The aim of this study was to investigate some of the genetic bases of WM capacity in childhood and to identify their influence on structural maturation and activation of the cortex. Candidate genes were selected on the basis of their previous association to learning and memory or to ADHD. The genes associated with ADHD were included with the hypothesis that these might be related specifically to the cognitive aspects of this disorder (4,9). Fifty-five single nucleotide polymorphisms (SNPs) within 18 candidate genes were selected for study (Supplement 1, Table S1).

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Received Jan 29, 2010; revised July 5, 2010; accepted Jul 30, 2010.

Methods and Materials

Participants—Community Sample

Participants in nine age groups (6, 8, 10, 12, 14, 16, 18, 20, and 25 years) were recruited using random sampling from the population registry in the town of Nynäshamn in Sweden. Exclusion criteria were first language other than Swedish, diagnosis of neurological or psychiatric disorder (with exception of ADHD or dyslexia), or a vision or hearing impairment judged to affect test performance. Out of 1012 contacted individuals, 380 agreed to participate and 335 were eventually included for behavioral and genetic testing. Parents' report of the child's and parent's ethnicity showed that in the majority (88.7%) of cases, both the participant and his or her parents were born in Sweden; 9.3% had at least one parent who was born outside of Sweden but within Europe, and the remaining 2% had one or two parents who were born outside of Europe.

Out of the original 335 participants, a blood or saliva sample was not obtained from one participant and genotyping failed for DNA from four participants, leaving available behavioral and genetic data from 330 participants (167 females; see Supplement 1, Table S2). Of the original 335 participants, 90 were randomly selected to participate in the imaging part of the study, which included both functional magnetic resonance imaging and T1-weighted structural imaging. Two participants withdrew from this part of the study (Supplement 1, Figure S1). Informed consent was obtained from each participant and from the parents of children younger than 18 years. The study was approved by the local ethics committee of the Karolinska University Hospital.

Participants— 4-Year-Old Sample

For the second, independent sample, data from 4-year-old children participating in an unrelated study were included. Participants were recruited through advertising in local newspapers, contacting preschools, and distributing flyers. One hundred twelve children

0006-3223/$36.00
doi:10.1016/j.biopsych.2010.07.036

participated; however, eight of these did not complete the visuospatial WM task included in the analysis. Moreover, DNA was unavailable for 16 children, 11 of whom withdrew their participation before DNA samples had been collected and five of whom withdrew from leaving blood or saliva samples. Thus, complete behavioral and genetic data were available from 88 participants (38 females) aged 47 to 57 months (mean age = 51.2, SD = 3.0). Behavioral assessments were done at the Karolinska University Hospital. The study was approved by the local ethics committee and parents' informed consent was obtained before testing for all participants.

Assessments of Working Memory and Other Cognitive Functions—Community Sample

All behavioral assessments except for the reading comprehension task were individually administered in a quiet room at the child's school. The reading comprehension task was administered either individually or in groups of 2 to 20 participants in a classroom setting.

Visuospatial WM was assessed using a visuospatial grid task from the Automated Working Memory Assessment battery (10), which involves remembering the location and order of dots displayed sequentially in a four-by-four grid on a computer screen. Verbal WM was assessed by a backward digit recall task, where numbers were read aloud to the participant who had to repeat them verbally in the reverse order. For both this test and the dot matrix test from the Automated Working Memory Assessment, difficulty was increased by one level (number of items to be remembered) after four trials were correctly answered on one level. Tests terminated after three errors were committed on one level. The score used was the total number of correct trials. The third WM task was a three-back task in which a total of 20 Swedish words were read to the participants, who were asked to indicate whether the word was the same as three words previous. Thus, a response of either "yes" or "no" was required for each item. A score was calculated using the number of correct "yes" responses minus the number of "false alarms," that is, the number of times the participant erroneously responded "yes."

Reasoning ability was assessed using Raven's Progressive Matrices (11). Participants in the youngest (6-year-old) age group performed subtests A through D, and all other participants performed all subtests (A through E). To account for these differences in administration, scores were calculated according to item–response theory using a partial credit model.

Speed of processing was measured using a letter–digit substitution task. In this task, the participants were shown a row with nine consonants, each paired with a number. Underneath, nine additional rows of 15 letters were presented with the numbers absent. The task was to pair as many numbers with their corresponding letter as possible during a 1-min period.

To measure reading comprehension, narrative and expository texts from the Progress in International Reading Literacy Trend Study (PIRLS 2001 T) and The International Association for the Evaluation of Educational Achievement Reading Literacy Study 1991 (12) were used. Seventy-seven items were used to form four age-adapted reading comprehension tests for 8 to 25 years olds.

Assessments of Working Memory and Other Cognitive Functions— 4-Year-Old Sample

A visuospatial WM task was presented with E-Prime software (13), using the design and scoring method described in previous work (14). It consisted of a computerized four-by-four grid in which the positions of sequentially presented dots were to be remembered. Nonverbal reasoning was assessed using Raven's Coloured Progressive Matrices (11). To improve the distribution of the visuospatial WM data in this sample, scores were transformed using the natural logarithm. The transformed measure was then used as the dependent variable in a linear regression analysis, with significance levels based on two-tailed analyses.

SNP Genotyping

In both cohorts, material for DNA extraction was collected either by blood or saliva samples. Genotyping was performed using matrix-assisted laser desorption/ionization-time of flight mass spectrometry (Sequenom, San Diego, California; http://www.sequenom.com) by the iPLEX method according to the manufacturer's instructions. Assays for all SNPs were designed using SpectroDesigner software (Sequenom). The mass spectra were analyzed for peak identification using the SpectroTyper RT 3.3.0 software (Sequenom). For every SNP, two independent scorers confirmed all genotypes, and regenotyping of 5% of the study samples resulted in 100% concordance. To ensure that each marker was within allelic population equilibrium in our control sample set, Hardy–Weinberg equilibrium (HWE) tests were carried out. For testing HWE, a p value threshold of .05 is considered too stringent for dropping SNPs, when several SNPs are genotyped (15). Instead, SNPs were considered not to deviate from HWE if $p > .005$. The overall genotyping success rate was $>$ 91% in the community sample and $>$ 95% in the 4-year-old sample (more details on genotyping procedures are available in Supplement 1).

Statistical Analyses—Community Sample

A latent variable analysis was carried out using the software Amos for Windows (version 16.0.1), in which the three WM tests were modeled as independent linear functions of a continuous latent variable. The latent variable was in turn modeled as a linear function of age in months and one genotype (coded as a continuous variable of 0, 1, or 2, representing the number of copies of a specific allele). The model was fitted for each of the 55 SNPs. All other statistical analyses were performed using SPSS for Windows (Rel. 16.0, SPSS). The effect of genotype on each of the WM tests and on the additional cognitive tests was assessed using linear regression and all reported significance levels are based on two-tailed analyses. For each test, performance scores were included as the dependent variable and age (in months) and genotype were included as independent variables.

Brain Imaging

For the structural analysis of gray matter density, T1-weighted spin echo images were acquired with a 3D MPRAGE sequence (field of view = 256 × 256 mm, 256 × 256 grid, 1-mm^3 voxel size) with a 1.5-T scanner. Following segmentation of the T1-weighted images, high-dimensional normalization was performed using the Diffeomorphic Anatomical Registration using Exponentiated Lie algebra (DARTEL) (16) the modulated, warped gray matter images were then smoothed with an 8-mm Gaussian kernel.

During functional magnetic resonance imaging (fMRI) scanning, participants completed two sessions (4 min 54 sec each), each consisting of 16 WM trials and 16 control trials in a pseudo-random order. In the WM trials, a series of yellow circles (either two or four) appeared sequentially within a four by four grid. After presentation, a cue consisting of a number and a question mark was presented within one of the grid positions. The number referred to the serial position in the previous stimulus sequence, and the participant was asked to indicate with a yes–no response whether the number and the grid position matched. For example, "2?" in a certain grid posi-

tion would ask participants to indicate whether the second circle had appeared in the grid position indicated. In the control condition, two or four red circles were presented in the corners of the grid. The cue in the control condition was always the number 8 presented in a noncorner space, and always required a "no" response. Only data from correct trials were included in the analysis. Preprocessing included slice-time correction, motion correction, normalization based on registration of the segmented T1-weighted image to gray and white matter templates (interpolating to 2-mm cubic voxels), and spatial smoothing with a 12-mm Gaussian kernel. For each subject, an image representing blood oxygen level-dependent (BOLD) signal during WM minus control was created and used in the second-level statistical analysis. Statistical analysis of both fMRI and structural images was performed with SPM5 (http://www.fil.ion.ucl.ac.uk/spm) using cluster-level statistics with *p* values corrected for the exploratory analysis performed in the entire brain (more details on imaging procedures and analyses are available in Supplement 1).

Results

Genetic Association to Working Memory in the Community Sample

With a strict threshold controlling for the multiple comparisons carried out, 1 of the 55 SNPs, rs363039 (with allele frequencies .31 and .69, respectively) was found to be significantly associated to the latent WM variable ($p = .0006$; $p < .05$ after correction for multiple comparisons). This SNP is located in intron 1 of the gene coding for the synaptosomal-associated protein, 25 kDa (*SNAP25*; Supplement 1, Table S3). Post hoc tests showed that the association was mainly driven by the visuospatial WM task ($p = .00005$), with a standardized beta-coefficient (the improvement in standardized visuospatial WM score for each additional copy of the A allele) of .17. Furthermore, in five of seven age groups, the behavioral effect increased monotonically with each additional copy of the A allele, and the mean advantage of having two A alleles compared with none was equivalent to 2 years of development in WM capacity (Figure 1). There were no significant interactions with age or sex.

Genetic Association to Further Cognitive Functions in the Community Sample

To assess the specificity of this association to visuospatial WM, additional association analyses between rs363039 genotype and performance on other cognitive tasks considered highly dependent on control of attention or WM and which were part of the larger testing battery were carried out. Significant association was found for nonverbal reasoning ($p = .0004$), reading comprehension ($p = .008$), and speed of processing ($p = .009$). For all significant associations the A allele was linked to superior performance.

Genetic Association to Cognitive Performance in the 4-Year-Old Sample

To confirm the association between visuospatial WM and rs363039, an analysis of the same SNP was carried out in the independent sample of 88 healthy 4-year-old children (*n*s for the rs363039 genotype groups were as follows: A allele (AA) = 10, AG = 44, and GG = 34). Again, the A allele was found to be the beneficial allele with a standardized beta-coefficient of .19 ($p = .07$). The genetic effect was thus equally strong in this group of children as in the community sample (age 6–25), although the statistical significance was weaker due to the smaller sample size. No association was found with a nonverbal reasoning task in this sample (standardized beta-coefficient = –.03; $p = .80$).

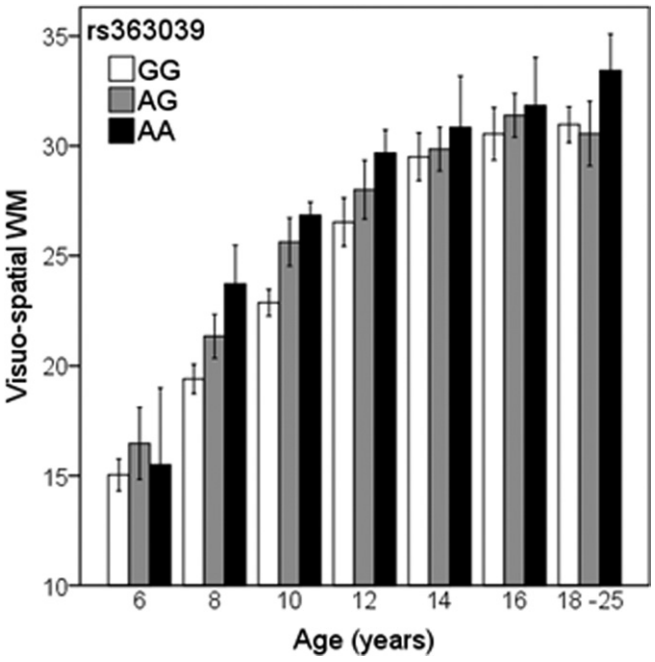

Figure 1. Effect of *SNAP25* polymorphism rs363039 on working memory (WM) performance. Performance on a visuospatial WM task (raw scores) for the various age groups, categorized according to rs363039 genotype (± SEM).

Voxel-Based Morphometry

High-resolution, structural T1-weighted MR images were obtained from 88 participants. Because of technical difficulties, data from 4 participants were lost, and data from 20 participants were excluded because of artifacts; thus, data from 64 participants remained for voxel-based morphometry analysis. Gray matter density was analyzed using voxel-based morphometry (16,17) and a general linear model including age, genotype, and age by genotype as independent factors. The main effect of genotype was not significant, but a significant interaction between the genotype and age was found in a region centered in the posterior cingulate cortex (PCC), corresponding to ventral and dorsal parts of Brodmann area 23 (18) (Figure 2A; $p = .003$, corrected at the cluster level) (19). Further analyses were performed controlling for the effect of gender on gray matter density. This revealed a significant main effect of gender ($p = .043$), with males showing higher mean gray matter density in the area of interest. There was no significant interaction between gender and genotype at rs363039, nor did inclusion of gender in the model explain the genotype's contribution to the outcome. The mean gray matter density of this region was extracted from each individual and plotted according to age group and genotype (Figure 2B), demonstrating the age dependent effects of the three alleles. In addition, the extracted values of gray matter density were correlated with performance on the visuospatial WM task. Significant correlations were seen for the youngest age group only, with correlations decreasing with increasing age (Figure 3). The behavioral association of the rs363039 genotype to visuospatial WM performance remains significant in this smaller subsample (standardized beta = .255, $p = .019$).

Functional Magnetic Resonance Imaging

Analysis involving genetic data and fMRI included 79 participants, 13 with one session (73 right-handed, six left-handed) (see

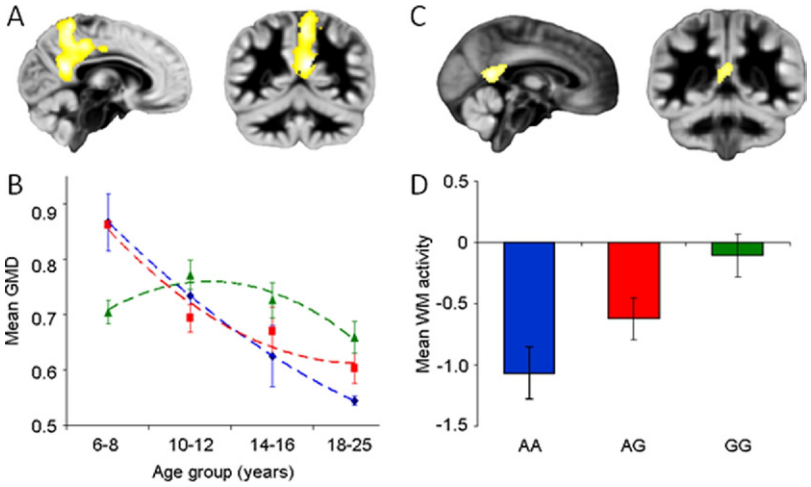

Figure 2. Effect of the *SNAP25* polymorphism rs363039 on structural maturation and brain activity. **(A)** Interaction between genotype at rs363039 and age on gray matter density (GMD). The significant cluster is superimposed on the mean reformatted, unsmoothed, gray matter image from the 64 individuals included in the analysis. Maximum correlation at coordinates x = 6, y = –51; *z* = 18. **(B)** Mean GMD in the posterior cingulate cortex (PCC) for each age group and genotype (AA shown as blue diamonds, *n* = 12; AG as red squares , *n* = 19; GG green triangles, *n* = 33). Dashed lines indicate second order fit; **(C)** Significant correlation between genotype at rs363039 and mean working memory (WM)-related brain activity in the PCC, superimposed on mean gray matter image. Maximum correlation at coordinates x = –4; y = –50; *z* = 14. **(D)** Mean WM activity (WM minus control) in the PCC region of interest for each genotype (AA, *n* = 12; AG, *n* = 23; GG, *n* = 44). Error bars in panels B and D represent SEM, estimated for each age group independently.

Supplement 1 for details of excluded data). The WM-related BOLD signal (WM activity minus control activity) in the entire brain was analyzed using regression modeling with age, genotype and age by genotype as independent factors. Genotype at rs363039 significantly predicted activity in one area of the brain, located in the PCC (ventral Brodmann area 23) and overlapping in location with the regions found in the analysis of gray matter density ($p = .03$, corrected at the cluster level; Figure 2C). Associations with genotype were also seen in the left frontal lobe, but this did not reach significance after correction for multiple comparisons (see Supplement 1). Individuals homozygous for the beneficial A allele (AA) showed larger mean deactivation (relative to the control condition) of the PCC during performance of the WM task (Figure 2D). Furthermore, mean levels of deactivation of the PCC decreased monotonically with numbers of G alleles. There were no significant effects of gender on BOLD signal. As in the whole population, in this subsample, there was a significant association between the genotype and visuospatial WM performance measured outside the scanner (standardized beta = .265, $p = .003$). WM performance during scanning correlated significantly with activity in the PCC when all age groups were combined ($r = –.30$, $p = .007$). However, when analyses were performed for the different age groups separately, the correlation was significant for the youngest age group (6–8 years, *n* = 20) only, $r = –.64$, $p = .002$. The correlations were negative, with better performance associated with lower activity in the PCC during the WM task compared with the control task.

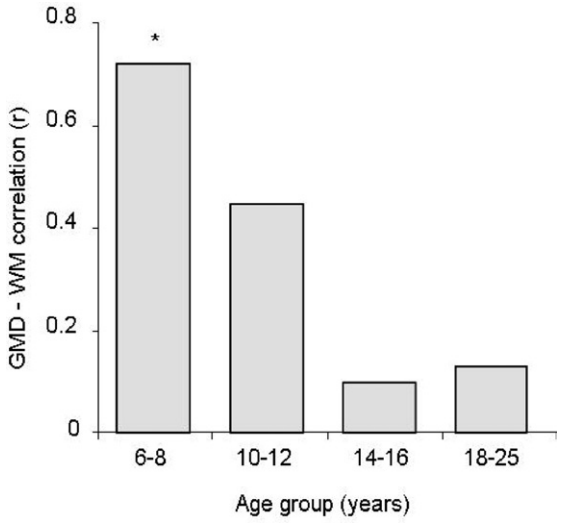

Figure 3. Correlations between gray matter density (GMD) in the posterior cingulate cortex and visuospatial working memory (WM) scores according to age group. *$p < .05$.

Discussion

An SNP, rs363039, located in intron 1 of the gene coding for the synaptosomal-associated protein, 25 kDa (*SNAP25*; Supplement 1, Table S3) was found to be significantly associated with both cognitive performance and structural maturation of gray matter and functional activity in the PCC.

The PCC is a central part of what has been termed the "default mode network," a set of regions preferentially active when individuals are not focused on the external environment (20–22). The PCC has a high degree of connectivity, as well as a high metabolic rate, compared with other cortical regions (23). Increased activity in PCC has been observed during lapses of attention, and decreased activity in this region is related to increased performance on cognitive tasks, including WM (24,25). Thus, it would be assumed that the ability to decrease activity in these regions during performance of a cognitively demanding task is important for actual task performance. Our line of observations supports this suggestion. As expected, mean activity in the PCC was found to be higher during the control task compared with the WM task. Furthermore, the degree to which this deactivation was observed was related to genotype at rs363039, with deactivation increasing monotonically with numbers of A alleles. Thus, individuals homozygous for the A allele showed the highest degrees of deactivation, consistent with the association of this allele to increased cognitive performance outside the scanner. An effect on the default network would presum-

ably affect performance on a wide range of cognitive tasks. This is supported by our findings of genotype associations with not only WM but also other cognitive measures requiring controlled attention.

The overall decrease of gray matter density in the PCC observed here is consistent with previous findings (26). The effect of *SNAP25* on gray matter density was age dependent with different directions of association for different age groups (Figure 2A and B). This age dependency might reflect a genetic effect on the trajectory of gray matter thickening and thinning during development, with the AA and AG groups having an earlier decrease in gray matter density compared with the GG group. The trajectory of gray matter thickening and thinning has previously been shown to vary with intelligence levels (27). Gray matter density in the PCC was significantly correlated with WM performance in the youngest age group but not in the older age groups (Figure 3). This suggests that the behavioral effects of *SNAP25* in older subjects, seen in both this (Figure 1) and previous studies (28–32), might result from an effect on childhood brain development. However, it is important to note that these findings are based on cross-sectional findings only, and any inferences about development can only be made with confidence once longitudinal data are available.

Abnormalities in the structure or connectivity of the PCC have recently been hypothesized to be one of the underlying neural aspects of ADHD (33) as well as schizophrenia (23). Functional MRI studies of individuals with ADHD have shown decreased functional connectivity within the network (34) and decreased levels of task induced deactivation of areas including the PCC. The suggested association between the PCC and ADHD is strengthened by the observation that patients with ADHD increase their levels of deactivation to reach those of control subjects when given stimulant medication (35).

It is at present not clear why the PCC would be especially sensitive to the expression of *SNAP25*. However, it is known that the PCC differs from many other brain areas in that it has a higher metabolism and an unusually high degree of connectivity (22,36). Although other areas are most likely also affected by its expression, such effects did not reach significance with the methods and thresholds used.

The SNAP-25 protein, a t-SNARE protein, has a crucial function for vesicle fusion in the presynaptic membrane (37) and plays an important role for neurite elongation during development (38). Mouse studies have revealed two isoforms of the SNAP-25 protein, SNAP-25a and SNAP-25b, in which the "a" form is most highly expressed early in life and the "b" form in adulthood (39). Mouse mutants deficient of SNAP-25b expression show impairments of neuronal development, short-term synaptic plasticity, and cognitive function (40). The switch in expression of the *SNAP25* from the a to the b form could thus be related to the age-dependent effect on structural brain maturation noted here (Figures 2 and 3B); however, further studies are needed to characterize how and when this change in expression occurs in humans.

Because rs363039 locates in the large intron 1 of *SNAP25*, one could hypothesize that it might affect regulatory DNA elements regulating its gene expression. In silico, we searched for transcription factor binding sites in close vicinity to this polymorphism using both the Genomatix suite (http://www.genomatix.de) and the transcription element search system (http://www.cbil.upenn.edu/cgi-bin/tess/tess) prediction programs. The A allele of rs363039 introduces a DNA binding site for glucocorticoid receptor but it also removes (compared with the sequence containing the G allele) a P53 half site as well as a binding site for zinc finger protein SZF1. These predictions would have to be confirmed in vivo and studied for understanding the functional role of this polymorphism.

The *SNAP25* gene has previously been repeatedly associated with ADHD (31), but a link to schizophrenia has also been suggested (30,32). The association between the polymorphism of the *SNAP25* gene and WM capacity is thus consistent with many of the previous associations reported for this gene because in both ADHD and schizophrenia, impairment of WM is one of the core cognitive deficits (5,6).

The SNP rs363039 along with other polymorphisms on the *SNAP25* gene have previously been associated with intelligence within a normal population of Dutch children and adolescents (aged 8 to 15 years) and adults (28,29). However, in these reports the G allele of rs363039 was found to be associated with higher scores on both the verbal and performance subtests of the Wechsler Intelligence Scale for children or adults (28,29). Thus, our results are pointing in the opposite direction to this prior study, because in the current study, the A allele was associated with not only superior WM performance but also higher performance on fluid intelligence (measured by Raven's progressive matrices). What underlies these conflicting findings remains an unresolved question.

To conclude, our results can connect and explain previous observations in showing that the *SNAP25* polymorphism in a normal population particularly relates to the PCC and WM, both of which, similarly to *SNAP25*, are believed to be involved in ADHD symptoms. It is for future clinical studies to decide whether the genotype's effect on cognitive capacity might, at least in part, provide an explanation for the association of *SNAP25* to ADHD. Similarly, the effects of the *SNAP25* polymorphism might serve as a piece of the puzzle linking ADHD and the default mode network.

We have identified a novel functional network connecting a genetic polymorphism with structural development of a specific brain region and cognitive functions. Identifying and understanding such functional networks is crucial for understanding both normal cognitive development and cognitive disorders.

We thank Jens Gisselgård, Ylva Samuelsson, Douglas Sjöwall, and Sissela Bergman Nutley for help with study administration; Kerstin Eriksson and Tomas Jonsson for scanning; and the Mutation Analysis Core Facility (MAF) at the Karolinska Institute. This work was supported by Knut and Alice Wallenberg Foundation, the Swedish Research Council, and a Swedish Royal Bank Tercentennial Foundation grant in the program "Learning and Memory in Children and Young Adults" to TK and JK. SS and FM were partly funded by Frimurarna Barnahuset, and KH was funded by the Swedish Research Council (Grant No. 523-2006-972).

The authors report no biomedical financial interests or potential conflicts of interest.

Supplementary material cited in this article is available online.

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