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Psychostimulant treatment and the developing cortex in Attention-Deficit/Hyperactivity Disorder

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Abstract

Objective—While there has been considerable concern over possible adverse effects of psychostimulants on brain development, no prospective study has examined this issue. We determined whether psychostimulant drug treatment for Attention-deficit/Hyperactivity Disorder (ADHD) was associated with differences in the development of the cerebral cortex during adolescence.

Method—Change in cortical thickness was estimated from two neuroanatomic magnetic resonance images on 43 subjects with DSM-IV ADHD (mean age at first scan 12.5 years (SD 2.1); second scan 16.4 (SD2.4). Nineteen subjects not treated with psychostimulants between the scans were compared with an age matched group of 24 subjects who received psychostimulants. Further comparison was made against a template derived from 620 scans on 294 typically developing children.

Results—Treatment defined ADHD groups differed in rate of change of cortical thickness of the right motor strip, the left middle/inferior frontal gyrus; and the right parieto-occipital region ($t(41) = 2.8$, $p=0.009$) The group difference was due to more rapid cortical thinning in the group 'off' psychostimulants (mean cortical thinning of 0.16mm/year, SD 0.17) compared to the 'on' group (thinning of 0.03 mm/year, SD 0.11). Comparison against a typically developing cohort showed the cortical thinning in the 'off' psychostimulants group was in excess of age appropriate rates. Treatment groups did not differ however in clinical outcome.

Conclusions—There was no evidence that psychostimulants were associated with 'slowing' of overall growth of the cortical mantle.

Introduction

Psychostimulant treatment of ADHD represents the largest single class of psychotropic medication prescribed to children in the US, with around 9% of all boys and 4% of girls receiving this medication (1). The long-term safety of psychostimulants is thus of great importance (2). Two recent large randomized trials showed psychostimulants suppress growth rates during treatment, with a decrease of 1.3cm/year in height, and between 1.3 kg/year (for pre-school age) and 2.5 kg./year (for school age children) in weight from age appropriate growth rates (3,4). This raises the question of whether there might be similar effects on human brain development.

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Meta-analysis of previous neuroanatomic studies finds that ADHD is characterized by a reduction in grey and white lobar volumes, with some prefrontal cortical regions being particularly affected (5). However, there are few studies of the structural correlates of psychostimulant treatment. Castellanos and colleagues found that prior treatment with psychostimulants in children with ADHD was associated at study entry with greater white matter lobar volumes relative to stimulant naive children with ADHD, and volumes which lay closer to the range of their typically developing counterparts suggesting a neuroprotective effect (6). An independent study of 30 children with ADHD examining regions implicated in the pathogenesis of the disorder similarly found that treatment with psychostimulants was associated with a more normative volume of the caudate and anterior cingulate cortex (7). While informative, these studies were cross sectional, limiting inferences that can be made about the developmental effects and only examined change either within *a priori* regions of interest or at the level of entire lobes.

We recently reported evidence of a delay in cortical maturation in ADHD by examining the age at which cerebral cortical points reached their peak thickness- that is the point at which childhood cortical thickening gave way to thinning (8). Whereas typically developing children without ADHD reached peak cortical thickness in the frontal cortex around age 7–8, in ADHD this developmental milestone was reached later at around age 10–11. Throughout adolescence both children with ADHD and healthy children show cortical thinning throughout nearly the entire cortex. We now ask if treatment with psychostimulants affects these developmental trajectories. We selected a subset of subjects from our cohort who had repeated neuroanatomic imaging, and were either treated (‘on’) or not treated (‘off’) with psychostimulants between scans. Most of ADHD subjects who were ‘off’ psychostimulants were between 9 and 20 years old and we thus confined our examination to this age range. Comparison was made against both an age matched group of ADHD subjects who received psychostimulant treatment between both scans and a cohort of typically developing children (9). All data thus lay within a period of cortical development predominately characterized by thinning.

This is the first prospective study to examine whether cortical development reflects differing treatment with psychostimulants.

Methods

Subjects

Subjects with ADHD were drawn from our cohort of 223 children with ADHD, diagnosis being based on the Parent Diagnostic Interview for Children and Adolescents (10), Conner’s Teacher Rating Scales (11), and the Teacher Report Form (for further details of the entire cohort see (6,8,12,13). Inclusion criteria for the current study were the availability of at least two neuroanatomic scans (leading to exclusion of 112 subjects) and of treatment histories from research case notes (leading to exclusion of a further 32 subjects). This left 79 eligible participants with ADHD. Twenty seven subjects were not treated with medication between two scans and most of the scans on this group were acquired between the ages of 9 and 20 years old and data beyond these limits was sparse. We thus confined the study to this period of greatest data density. From the 52 subjects with ADHD who were treated between the two scans we selected an age matched group of 24 subjects (the remaining subjects had data lying outside the age range). Thus the groups ‘on’ and ‘off’ treatment between scans did not differ significantly in age. All children selected for this study had combined type ADHD.

The study comprised an initial day hospital assessment phase. Children were then discharged to their treating physicians in the community and decisions regarding psychostimulant treatment during this period were the joint responsibility of children, their families and physicians.

The cortical development of the ADHD groups were compared against a template of cortical development derived from 294 typically developing controls who contributed 620 neuroanatomic magnetic resonance scans, reported upon previously – see reference (9). These children were matched in IQ and gender composition with the ADHD group, given the impact of both these variables on cortical development (9,14). The institutional review board of the National Institute of Health approved the research protocol and written informed consent and assent to participate in the study were obtained from parents and children, respectively.

Neuroimaging

T1-weighted images with contiguous 1.5-mm slices in the axial plane and 2.0-mmslices in the coronal plane were obtained using 3-dimensional spoiled gradient recalled echo in the steady state on the same 1.5-T General Electric Signa scanner (Milwaukee, WI). (echo time of 5 ms, repetition time of 24 ms, flip angle of 45°, acquisition matrix of 256 × 192, number of excitations equals 1, and 24 cm field of view). Native MRI scans were registered into standardized stereotaxic space using a linear transformation and corrected for non-uniformity artifacts (15). Registered and corrected volumes were segmented into white matter, gray matter, cerebrospinal fluid and background using an advanced neural net classifier (16). To determine cortical thickness, a surface deformation algorithm was applied which first fits the white matter surface, then expands outward to find the gray matter-CSF intersection defining a known relationship between each vertex of the white matter surface and its gray matter surface counterpart. Cortical thickness can thus be defined as the distance between these linked vertices (a total of 40,962 such vertices are calculated) (17). White and grey matter surfaces were re-sampled into native space by inverting the initial stereotaxic transformation. Cortical thickness was then computed in native space. In order to improve the ability to detect population changes, each subject's cortical thickness map was blurred using a 30mm surface based blurring kernel (18). A 30-mm-bandwidth blurring kernel was chosen on the basis of population simulations indicating that this bandwidth maximized statistical power while minimizing false positives (18). This kernel also preserves the capacity for anatomical localization as 30-mm blurring along the surface using a diffusion smoothing operator represents considerably less cortex than the equivalent volumetric Gaussian blurring kernel as it preserves cortical topologic features (18).

Statistical analyses

The primary variable of interest was the rate of change in raw cortical thickness, calculated as:-

$$\text{Rate of change} = (CT_2 - CT_1)/(age_2 - age_1)$$

where CT is the thickness (in mm) of each cortical point at the first (age_1) or second scan (age_2). The results of the cortical thickness analyses were visualized through projection onto a standard brain template, showing regions where treatment group differences in the rate of change of cortical thickness differed significantly in a t test for independent samples at an uncorrected $p<0.05$. Such visualization showed clustering of the cortical points with group differences and further analyses retained those clusters with a spatial extent of more than 50 vertices, and the mean cortical thickness of each cluster was used in further analyses.

Cortical thickness values of the ADHD groups were then contrasted against a template of typical cortical development, whose derivation has been described in detail elsewhere (9). From this template we estimated the expected cortical thickness for a typically developing child at the mean age of the first and second scan.

Results

Demographic and clinical characteristics

The treatment-defined ADHD groups did not differ significantly with respect to age, gender composition and IQ nor in clinical characteristics - see Table 1. Outcome data at the time of the second scan was available on 35 of the 43 subjects. Neither the proportion of subjects retaining a diagnosis of combined type ADHD at follow-up nor a measure of global functioning differed significantly between groups.

Neuroanatomic

The medication-defined ADHD groups differed significantly in the rate of change of cortical thickness in the left middle/inferior frontal gyrus ($t(41)=2.5$, $p=0.02$), the medial and inferolateral aspect of the right precentral gyrus ($t=2.5$, $p=0.02$), and the right parieto-occipital region ($t=2.3$, $p=0.02$). Averaging the cortical thickness across all these regions, the significant difference ($t=2.8$, $p=0.009$) arose from more rapid cortical thinning in the group stopping psychostimulants, at a mean rate of loss of −0.15 mm/year (SD 0.17), compared to cortical thinning rate of −0.03 mm/year (SD 0.11) for the 'on' psychostimulants group. The impact of these different rates of change on cortical thickness values at baseline and the endpoint are shown in Figure 1. At baseline there were no significant group differences, however by endpoint the group 'off' psychostimulants had a significantly thinner cortex than the 'on' group. All results held when gender and IQ were entered as covariates. The differential rates of cortical change in the left frontal and right medial prefrontal/motor, but not the right posterior parieto-occipital regions held after entering covariate medication history prior to the baseline scan (as lifetime total dose in methylphenidate equivalents) as a covariate.

We compared the effects of different classes of psychostimulants contrasting those taking methylphenidate preparations against those taking amphetamine based medication. The two subjects taking pemoline were excluded from this analysis. Examining the mean rates of cortical change across the regions shown in Figure 1, subjects taking methylphenidate had a rate of cortical thinning of 0.03 mm/year (SD 0.09), those taking amphetamine had a rate of thinning of 0.05 mm/year (SD 0.13), compared to a rate of cortical thinning of 0.16 mm/year (SD 0.15) for those who were 'off' psychostimulants ($F(2,38)=3.2$, $p=0.05$). The amphetamine and methylphenidate groups did not differ significantly from each other in rate of cortical change ($p=0.61$).

Discussion

There was no evidence that psychostimulants were associated with 'slowing' of overall growth of the cortical mantle- a notable finding given the reports of possible psychostimulant related slowing of height and weight gain in children and adolescents (3,4). Adolescents with ADHD untreated with psychostimulants showed regional decreases in cortical thickness relative both to their peers with the disorder who took psychostimulants and typically developing adolescents. However, the functional significance of the finding is unclear, partly as we did not collect cognitive data at both time points in most subjects. Additionally, it is important to note that the increased cortical thinning in the ADHD group stopping psychostimulants was not associated with any difference in clinical outcome. With these caveats in mind, it is still worthwhile to consider some possible interpretations. Psychostimulants tend to normalize goal-directed activity (19–22) and cognitive processes, including planning, cognitive flexibility, vigilance and response inhibition (23). In healthy adults, methylphenidate induced improvement in working memory is associated with alterations of cerebral blood flow in the left dorsolateral prefrontal, supplementary motor and posterior parietal cortex-overlapping in part with the regions we find to be differentially sensitive to psychostimulants (24). In children

with ADHD, psychostimulant induced improvement in the ability to inhibit prepotent responses is associated with increased frontal (and striatal) activity as assayed by functional MRI (25). In adults with ADHD, correction of executive deficits by psychostimulants is associated with altered prefrontal cortical activity- with increased activation of the premotor and decreased activation of the middle and medial prefrontal cortex (26). Thus, psychostimulant induced increase in age appropriate levels of cognition and action, and perhaps underlying localized fronto-parietal neural activity, might foster cortical development within the normative range. In this regard psychostimulant effects on the developing brain in ADHD can be conceptualized as an example of activity-dependent neuroplasticity. Additionally, it is possible that psychostimulants have a direct trophic effect on the cortex, particularly in view of the growing evidence for the role of catecholaminergic neurotransmitters in cortical development (27,28), although this explanation does not account for the highly regional effects detected.

The current study extends our previous demonstration of more normative white matter volumes in those with a history of psychostimulant use by demonstrating effects on gray matter morphology (6). Our longitudinal approach enabled detection of correlates of psychostimulant treatment on the rate of cortical development; this was not possible in our earlier cross sectional analysis that compared cortical thickness at study entry in groups with differing psychostimulant histories (13). **Additionally, by using the metric of cortical thickness, determined at over 40,000 cortical points, we were able to detect more localized changes missed by lobar volumetric studies. The 'on' and 'off' medication groups were age-matched to ensure that any differences in cortical trajectories are not confounded by age effects.**

In a recent study we demonstrated delay in cortical maturation in most of the frontal (excluding the sensorimotor region) and temporal cortex (8) using the age of attaining peak cortical thickness as a developmental marker. An assessment of whether psychostimulant treatment contributes to this phenomenon is limited as in the current study we focused on the adolescent phase of cortical thinning and did not examine the childhood phase of increase in cortical thickness. However some considerations argue against psychostimulants being a major factor in the altered timing of maturation. The regions that were sensitive to medication were highly focal, (unlike the disturbance in timing of maturation which involved most of the cortex) and encompassed areas with both late -the dorsolateral prefrontal regions-and early maturation - the motor regions.

At the time of the first scan (~12years) the ADHD medication groups did not differ significantly from each other in cortical thickness in the regions shown in Figure 1, perhaps reflecting their similar history of medication exposure prior to the first scan. In prefrontal regions, the typically developing group attains peak cortical thickness earlier and thus enters the phase of cortical thinning earlier than those with ADHD (see (8). However, the typically developing group also reaches a higher peak (i.e. a thicker cortex) and thus starts thinning from a higher baseline. By age 12, the ADHD and typically developing cohorts reported upon in (8) do not differ significantly in estimated cortical thickness in the prefrontal regions shown in Fig 1A.

In this observational study, it is important to consider the possibility that the group differences in cortical trajectories are attributable to other dimensions on which the groups differ. The groups did not differ in initial clinical characteristics or clinical outcome, removing the possibility that differences in the severity of the disorder or clinical course underpinned the findings. The groups also did not differ significantly on other variables known to affect cortical trajectories such as gender and intelligence. Of course the ideal design is a randomized trial comparing cortical growth in children on psychostimulants against an un-medicated comparison group- but this is both logistically and ethically challenging. Other limitations of

the current study include the lack of external validation of treatment histories which were based purely on patient and parent report. It is impossible to exclude neuroanatomic effects of the non-psychostimulant medication received by the ADHD groups, although the prevalence of such non-psychostimulant medication was low and did not differ between groups at the time of final assessment.

Within the inherent limitations of an observational study, we find highly regional differential associations between cortical development and psychostimulant treatment in ADHD which may reflect activity dependent cortical plasticity.

Acknowledgments

PS designed the study, conducted analyses and wrote the manuscript with JLR. WS was study coordinator, MM conducted data collection, KE provided technical support, LC was database manager; AE developed the neuroimaging tools used. PS and JLR had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. The research was funded by the Intramural Research Program at the National Institutes of Health, which played no role in the design and conduct of the study. The authors thank Xavier Castellanos for initiating the project and the young people and their families who participated in the study. The authors declare no conflict of interest.

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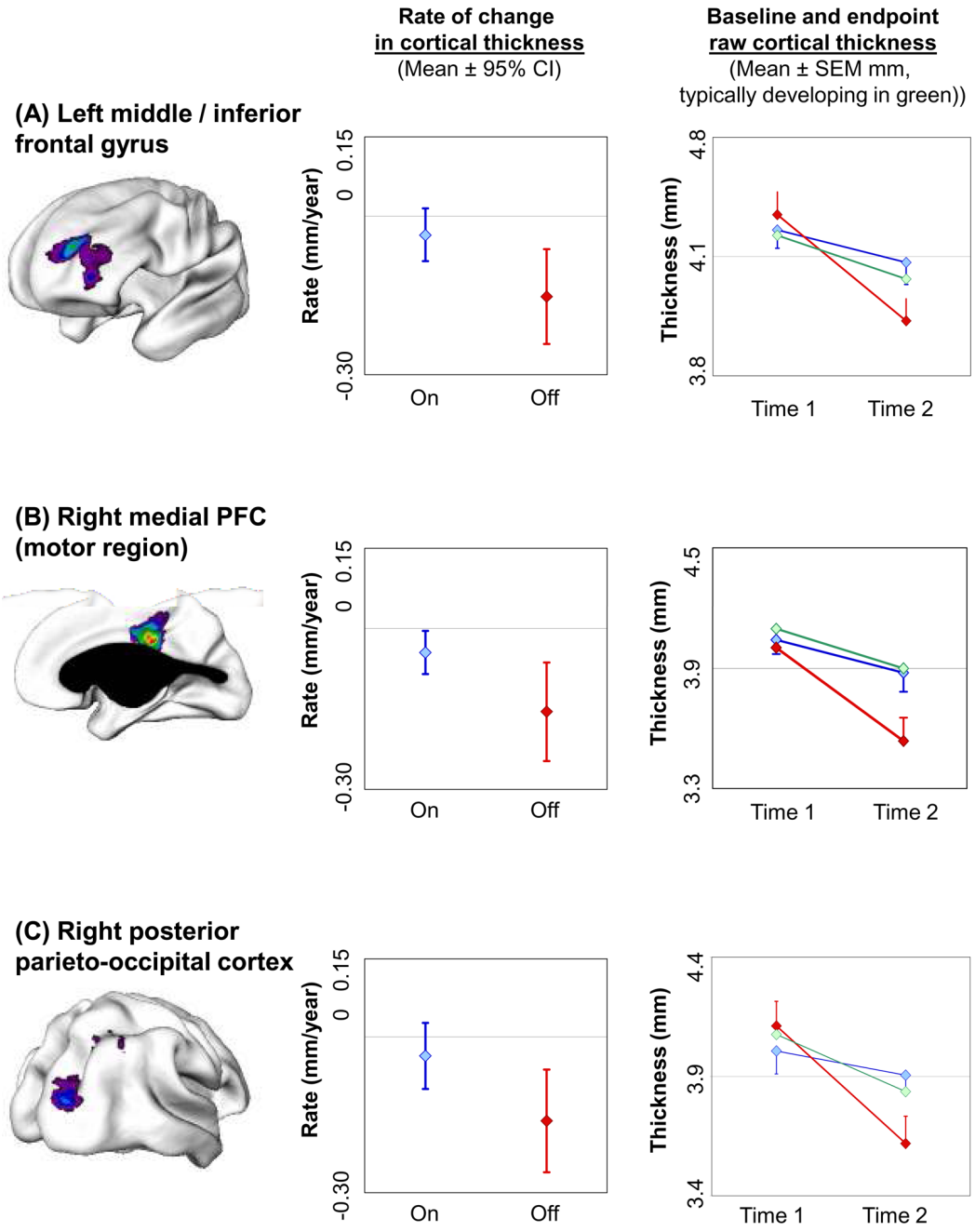

Figure 1.

Brain templates (leftmost) show the regions where the ADHD groups had a significantly different rate of cortical growth. The rate of change in raw cortical thickness in these regions is shown (middle column). The final column shows the baseline and endpoint raw cortical thickness for each ADHD group and the age expected values for a typically developing adolescent. The group 'on' psychostimulants is shown in blue, the group 'off' psychostimulants in red. The expected cortical thickness at time 1 (age~ 12.5 yrs) and time 2 (~age 16.4) for a typically developing group is given in green.

Table 1

At baseline, 40 of the 43 subjects were taking psychostimulants (23/24 (95.8%) in the group that remained 'on' psychostimulants during the study and 17/19 (89.5%) of those who then went 'off' psychostimulants- Fisher exact test p=0.58). At follow-up, eleven of the 24 subjects 'on' psychostimulants were taking methylphenidate preparations, eleven were on amphetamine preparations and two were on pemoline. The mean daily dose in methylphenidate equivalents was 35mg (SD 22; range 5mg to 85mg). Four subjects in the 'on' group were treated with second-line agents for ADHD (three with clonidine and one with guanfacine) and one subject in the 'off' psychostimulant group was treated for several months with guanfacine. Further, in the group 'on' psychostimulants, four were treated for depression (with desipramine, venlafaxine, sertraline and nefazodone), one for generalized anxiety disorder (with fluvoamine) and two for mood disorders NOS (both with sodium valproate). In the 'off' psychostimulant group, two subjects were treated for depression (with imipramine and buproprion) and one for a mood disorder NOS (with sodium valproate). The rates of comorbidity did not differ significantly between groups- Table 1.