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Atomoxetine與Methylphenidate對未用藥注意力不足過動症患童的長期療效之差異：數字Stroop測驗的功能性磁振造影研究

Differential chronic therapeutic effects of atomoxetine and methylphenidate on drug-naïve children with attention-deficit/hyperactivity disorder: a counting Stroop functional MRI study

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誌謝

I won’t be surprised if it’s a dream.

感謝命運的安排，讓我加入了高淑芬醫師的團隊，成就了碩士生活中的大小確幸。感謝高醫師在百忙中每一次的指導、鼓勵與關懷，感謝腦心所同學楊立光醫師碩士生涯的互相扶持，也感謝高醫師助理卉怡、鈺倫、雅珊、怡萱、 宇璇、淑嵐等學姐們的幫忙。感謝心理系指導教授周泰立老師對我的耐心與信任，研究室裡一起奮鬥和享樂的苓萱、允中、岱珊、芳葦、芳諭、佩宜，以及充滿愛與熱誠的品臻和姝慧學姐。這項研究的完成也必需感謝各位參與研究的個案與其家屬，謝謝高醫師和商志雍醫師嚴謹招收個案，也謝謝利霙和巧涵學姐在實驗設計和分析上的協助。另外，也謝謝曾文毅醫師、吳恩賜老師、藍先元醫師和丘彥南醫師在研究過程中給予的建議與教導。

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命運讓我在生命旅途中遇見你們，造就了這美好的兩年。偶爾想起，總覺得像是做了一場美夢。

中文摘要

研究目的：Atomoxetine 和 methylphenidate 是台灣以及許多其他國家用於治療注意力不足過動症（Attention Deficit/Hyperactivity Disorder, ADHD）僅有的兩種藥物。雖然這兩種藥物具有相似的藥效，過去許多臨床研究指出 ADHD 患者對這兩種藥物的臨床反應不盡相同，顯示兩者於藥理機制上具有差異存在。為了探討藥理機制和臨床藥效之間的關係，本研究作者觀察無用藥經驗的患童在長期接受藥物治療前後，在神經心理測驗及腦部活化程度的變化，以此針對兩種藥物進行直接比較研究。

研究方法：五十位未用藥 ADHD 患童（年齡介於 7 歲至 17 歲）被隨機分配服用 atomoxetine（n=25）或 methylphenidate (n=25)，療程為十二星期。這些研究參與者在療程前後各接受一次功能性磁振造影的掃描，並同時進行數字 Stroop 測驗。另外，他們在每次掃描後會進行 Conner's Continuous Performance Test (CCPT)，以評估其集中性注意力和衝動性在療程前後的變化。共有二十位 atomoxetine 療程的參與者，和二十二位 methylphenidate 療程的參與者完成最終的影像的分析。

研究成果：影像分析結果發現 atomoxetine 療程會降低背側前扣帶迴和背側前額葉皮質的活化程度，methylphenidate 療程則是提升額下葉的活化程度。另外，前者腦區活化程度的改變，與參與者在集中性注意力的進步呈現正相關，而後者則

與參與者於衝動性的減輕呈現正相關。

研究結論：本研究成果推論 atomoxetine 和 methylphenidate 於長期治療後的神經變化之差異，或許是導致每位 ADHD 患者對這兩種藥物臨床反應不一致的原因。

關鍵詞：數字 Stroop 測驗，功能性磁振造影，CCPT，衝動抑制，集中性注意力，atomoxetine，methylphenidate。

Abstract

Objective: Methylphenidate and atomoxetine are two primary medications approved for treating attention-deficit/hyperactivity disorder (ADHD). Despite comparable efficacy, clinical studies revealed a differential response of these medications, probably due to underlying distinct pharmacological mechanisms. To relate neural mechanisms to clinical efficacy, a head-to-head comparison study was conducted to discriminate changes in brain activation of drug-naïve children with ADHD when performing neuropsychological tasks after long-term pharmacotherapy.

Method: Fifty drug-naïve children with ADHD, aged 7 to 17, were randomized to 12 weeks of treatment with methylphenidate (n = 25) or atomoxetine (n = 25). They were scanned twice using functional magnetic resonance imaging (fMRI) during the counting Stroop task, before and after treatment. Their focused attention and impulsivity were also evaluated twice by the Conner's Continuous Performance Test (CCPT). The final sample for fMRI analysis consisted of 20 and 22 in the methylphenidate and atomoxetine groups, respectively.

Results: Atomoxetine down-regulated activations in the dorsal anterior cingulate cortex and dorsolateral prefrontal cortex, which were correlated with the improvement

in focused attention assessed by the CCPT. In contrast, methylphenidate up-regulated activation in the inferior frontal gyrus, which was correlated with decreasing severity of impulsivity assessed by the CCPT.

Conclusions: The current findings suggest that differential chronic therapeutic effects on neuronal changes induced by atomoxetine and methylphenidate may contribute to clinical improvement.

Keywords: counting Stroop fMRI; CCPT; inhibitory control; focused attention; atomoxetine; methylphenidate

1. Introduction

1.1 Attention-deficit/hyperactivity disorder (ADHD)

Attention-deficit/hyperactivity disorder (ADHD) is a common early-onset neuropsychiatric disorder (Gau *et al*, 2005) associated with lifelong deficits in a wide range of executive functions (Seidman, 2006), and long-term academic (Wu and Gau, 2013) and social impairments (Yang *et al*, 2013), which may be mediated by impaired executive functions (Tseng and Gau, 2013). Multiple neuropsychological pathological models of ADHD has been established in extensive literature (Nigg et al 2004, Sergeant 2000, Sonuga-Barke 2003). The dual pathway model (Sonuga-Barke 2003), one of the most influential models, proposed the executive and motivational dysfunction as the two complimentary pathways contribute to the pathology of ADHD. Our work focused on the executive pathway, where inhibition control appears to be most impaired among the wide range of executive dysfunctions (Barkley 1997, Willcutt et al 2005), and was even suggested as the primary core deficit in ADHD (Barkley, 1997).

1.2 Clinical and pharmacological differences between atomoxetine and methylphenidate

Atomoxetine and methylphenidate are two main medications approved for treating ADHD (Gau *et al*, 2007; Gau *et al*, 2006). Long term treatment with these medications is not only proven to be clinically efficacious (Gau *et al*, 2008; Gau *et al*, 2007), but also improves a wide range of executive functions and focused attention among children with ADHD (Gau and Shang, 2010; Shang and Gau, 2012). Two head-to-head comparison studies (Ni *et al*, 2013a, b; Yang *et al*, 2011, 2012) revealed that despite comparable improvement in inhibitory control and working memory, only atomoxetine

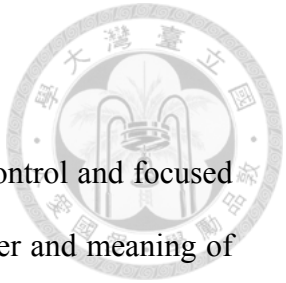
improved attention and visuo-spatial planning (Ni *et al*, 2013a) and only methylphenidate improved set shifting and verbal fluency (Yang *et al*, 2011). In addition, one-third of youths with ADHD responded better to one or the other in a cross-over study (Newcorn *et al*, 2008). This preferential response might be explained by distinct underlying pharmacological mechanisms. Both medications acutely increased extracellular dopamine and norepinephrine in the prefrontal cortex, but only methylphenidate increased dopamine in the striatum and nucleus accumbens (Bymaster *et al*, 2002). However, the increase of prefrontal norepinephrine induced by atomoxetine, but not methylphenidate, was reduced by chronic treatment (Koda *et al*, 2010), whereas the striatal neural activity was attenuated by chronic administration of methylphenidate (Brandon and Steiner, 2003; Chase *et al*, 2003), which might be due to the up-regulation of dopamine transporter availability (Sproson *et al*, 2001). Given much remains unknown about the manifestation of these neurochemical effects in behavioral and clinical performance, neuroimaging is one promising approach to address these questions.

1.3 Findings and limitations of previous imaging studies

Positron emission tomography (PET) studies on healthy participants revealed that methylphenidate blocked the norepinephrine transporter in locus ceruleus and thalamus (Hannestad *et al*, 2010), as well as the dopamine transporter in striatum, thus increasing striatal dopamine (Volkow *et al*, 2004). Moreover, chronic treatment with methylphenidate normalized structural brain changes in white matter, the anterior cingulate cortex, thalamus, and cerebellum in ADHD (Schweren *et al*, 2013). These findings, however, did not imply the presumed downstream functional cortical brain responses, which might directly contribute to the behavioral and clinical improvement.

Therefore, several task-based functional magnetic resonance imaging (fMRI) studies have explored brain activation changes induced by these medications. Acute up-regulation of prefrontal activation, particularly in the dorsolateral region, by atomoxetine was consistently observed in both boys with ADHD (Cubillo *et al*, 2013; Cubillo *et al*, 2014b) and healthy adults (Chamberlain *et al*, 2009; Graf *et al*, 2011), parallel to the aforementioned observation in animal models. Atomoxetine also acutely down-regulated activation in anterior cingulate cortex (ACC) in boys rather than adults with ADHD (Cubillo *et al*, 2013). However, acute up-regulation of fronto-striatal network, notably the inferior frontal gyrus (IFG) has been the most consistent findings of methylphenidate effect on inhibitory control in children with ADHD (Cubillo *et al*, 2014b; Rubia *et al*, 2011).

Despite several imaging studies of the methylphenidate and atomoxetine effects on brain functions, majority of these studies are limited by small sample size (range, 10-21, mean ± SD = 15.9 ± 3.8), only use of a single dose of methylphenidate (e.g., Rubia *et al* (2011) or atomoxetine (Cubillo *et al* (2013); Cubillo *et al*, 2014a; Cubillo *et al* (2014b)), and experiments conducted in healthy subjects (Chamberlain *et al*, 2009; Graf *et al*, 2011; Marquand *et al*, 2011). Only few studies examined the chronic treatment effect of methylphenidate (Bush *et al*, 2008; Schulz *et al*, 2012) and atomoxetine (Bush *et al*, 2013; Schulz *et al*, 2012) in separate studies with a relatively short duration of treatment (6-8 weeks). However, medications for ADHD are typically titrated and given over long periods of time, with the maximal behavioral efficacy of methylphenidate and atomoxetine at about 6 (Biederman *et al*, 2006) and 12 (Gau *et al*, 2010; Montoya *et al*, 2009) weeks, respectively. Therefore, this study aimed to disclose the differential underlying functional changes induced by these two medications that may contribute to the long-term clinical improvement.



1.4 Hypothesis of current study

We utilized the counting Stroop task to assess the inhibitory control and focused attention of participants in dealing with interference between number and meaning of the Chinese characters. Essential engagement of brain regions as our a priori hypothesis include ACC for response selection and error detection (as reviewed in Bush (2011)); IFG for response inhibitory control (as reviewed in Cortese *et al* (2012)); and dorsolateral prefrontal cortex (DLPFC) for performing the counting Stroop task (Bush *et al*, 1999; Bush *et al*, 1998). To explore how the functional changes observed at MRI assessment were associated with the treatment effects of the two medications, and two major behavioral aspects (i.e., focused attention and cognitive/behavioral impulsivity) determined by inhibitory control in ADHD (Barkley, 1997), the participants were also assessed by the Conners' Continuous Performance Test (CCPT) outside the MRI scanner. We hypothesized that atomoxetine would affect the activation in the prefrontal cortex and ACC, while methylphenidate might up-regulate activation in prefrontal cortex, particularly IFG, but not striatum.

2. Methods

2.1 Participants and procedures

Sixty-two eligible drug-naïve children were recruited from the Department of Psychiatry, National Taiwan University Hospital, Taipei, Taiwan. In addition to clinical assessments by two authors (CYS and SSG), their parents were interviewed by using the Chinese version of the Schedule for Affective Disorders and Schizophrenia for School-Age Children–Epidemiological Version (K-SADS-E) (Gau *et al*, 2005) by the corresponding author (SSG) to confirm ADHD diagnosis and to exclude any other psychiatric disorders. Of them, 12 were excluded from the study (see Figure 1for the reasons) and 50 children aged 7-17 (mean age ± SD = 10.3 ± 2.16; 42 males) with a clinical diagnosis of ADHD according to the DSM-IV diagnostic criteria (American Psychiatric Association, 1994) were assigned to receive a 12-week treatment with either osmotic release oral system (OROS) methylphenidate (n = 25) or atomoxetine (n = 25). All the participants either started to take OROS methylphenidate 18 mg/day or atomoxetine 0.5mg/kg/day in the morning at baseline. The investigators (CYS and SSG) would titrate the drug dosage at week 2 (usually reaching the optimal dose), week 4, and week 8 depending on clinical response and adverse effects (maximum daily dosages of OROS methylphenidate and atomoxetine were 54 mg/day and 1.2mg/kg/day, respectively, Figure 1). They performed the counting Stroop task at baseline during fMRI scan before initial dose of medications and at week 12. In order to achieve maximum efficacy, considering the pharmacokinetics of the two medications (Coghill et al 2013, Witcher et al 2003), participants were required to take medications as usual in the morning 2 to 4 hours prior to the 2nd fMRI assessments. The investigators assessed safety using a structured interview about all the potential adverse effects of

methylphenidate and atomoxetine. In the OROS methylphenidate group, two discontinued medication at week 2 and did not receive the 2nd fMRI assessments. Three of each treatment group had severe motion at fMRI assessments were also removed from the fMRI analysis, yielding the final sample of 20 and 22 for the OROS methylphenidate and atomoxetine groups, respectively (Figure 1, Table 1).

Twenty typically developing (TD) children with similar distributions of age, sex, and IQ of the ADHD group were recruited from a similar local community via school principals and teachers rather than through advertisement. TD children and their parents received the K-SADS-E interview to ensure that they neither had a history nor current diagnosis of ADHD and other psychiatric disorders. TD children then were scanned once to assure the directions of medication-induced changes in brain functioning in children with ADHD (Peterson *et al*, 2009). Detailed demographic and physical characteristics and other baseline information of all the participants are presented in Table 1.

All participants were native Mandarin-Chinese speakers with normal hearing and normal or corrected-to-normal vision. Participants with full-scale IQ less than 75 and a clinical diagnosis of systemic disease, neurological disorders or psychiatric disorders (except ADHD in the ADHD group) were excluded from the study. Informed consent was obtained after participants and their parents had received the detailed information of experimental purpose and administration. The informed consent procedures were approved by the Research Ethics Committee (ID: 200812153M; ClinicalTrials.gov number, NCT00916786) of the National Taiwan University Hospital, Taiwan before study implementation.

2.2 Clinical Performance

Clinical symptoms of participants with ADHD were evaluated before and after treatment, using the Clinical Global Impression-ADHD Severity (CGI-ADHD-S) rating scale by the investigators. The CGI-ADHD-S is a single-item rating of the clinician's assessment of the global severity of ADHD symptoms in relation to the clinician's total experience with ADHD patients. Severity was rated on a 7-point scale (from 1=normal, not at all ill, to 7=among the most extremely ill). The Chinese CGI-ADHD-S has been widely used in treatment studies on ADHD in Taiwan (Gau et al 2008, Gau et al 2007)

2.3 Conners' Continuous Performance Test (CCPT)

The CCPT is a 14-minute, widely-used computerized task for individuals aged 6 and up (Conners and Staff., 2000). Participants were required to respond when letters appeared on the screen except for letter X. There are 6 blocks in the CCPT, with 3 sub-blocks each containing 20-letter presentations, resulting in 360 trials in total. The sub-blocks differ in three inter-stimulus intervals (ISIs) of 1, 2, and 4 seconds with the display time of 250 milliseconds, and the sequence of ISI conditions is presented randomly. Among the CCPT indices, response style indicating response tendency of the participants is a function of the ratio of hit target (hit rate) to hit non-target (false alarm rate) stimuli (Egeland and Kovalik-Gran, 2010). For a participant who can focus on the target will not respond inappropriately and often obtain a higher value of this index; while for a participant who has impaired focused attention will respond more freely and is less concerned about failing resulting a lower value of response style. The perseveration is definied as the responses with reaction time less than 100 milliseconds, an index indicating the cognitive/behavioral impulsivity, which is highly related to inhibitory control (Egeland *et al*, 2010). The CCPT has been widely used to

measure focused attention and inhibitory control in ADHD (Gu *et al*, 2013; Hwang Gu *et al*, 2013; Lin *et al*, 2013; Wu *et al*, 2014).

2.4 Functional activation task

Experimental stimuli of the counting Stroop task were classified into the congruent, incongruent, and control conditions (Figure 2), with 24 trials in each condition. In the congruent condition, the number of words was consistent with the meaning of the word such as ‘‘one’’, ‘‘two’’, ‘‘three’’ or ‘‘four’’, but these were inconsistent in the incongruent condition. In the control condition, the meaning of words did not give any clue to number. The number of syllables, visual complexity (strokes per word), and frequency of all the words of the three conditions were well matched. Trials started with a solid square (500 msec), followed by sets of 1-4 identical words (3200 msec). There was a 200-msec blank between trials. Participants were required to report the number of words (one to four) via button-pressing, regardless of word meaning (Fan *et al*, 2014).

2.5 MRI image acquisition

Images were acquired using a 3 Tesla Siemens Tim-Trio scanner with the 32-channel head coil. Participants looked at the visual stimuli projected onto a screen via a mirror attached to the head coil. Each participant performed two 2.8-minute functional runs. In each run, 85 image volumes were acquired with echo planar imaging method to detect the BOLD (blood oxygenation level-dependent) signal. Functional images were interleaved from bottom to top collected parallel to the AC-PC plane. The scanning parameters were the following: repetition time (TR) = 2000ms; echo time (TE) = 24ms; flip angle = 90º; matrix size = 64 × 64; field of view = 25.6cm; slice thickness

= 3mm; number of slices = 34. A high-resolution, T1-weighted three dimensional image was also acquired (Magnetization Prepared Rapid Gradient Echo, MP-RAGE; TR = 2300ms; TE = 2.98ms; flip angle = 9º; matrix size = 256×256; field of view = 25.6cm; slice thickness = 1mm). The orientation of the 3D image was identical to the functional slices. In order to optimize the event-related design, the task stimuli were administered in a pseudorandom order for all participants (Burock *et al*, 1998).

2.6 Image and statistical analysis

Data analysis was performed using SPM8 (Statistical Parametric Mapping). The differences in slice-acquisition time of the functional images were corrected to the middle volume. These images were then realigned to the first volume in the scanning session using affine transformations. The exclusion criteria for motion were 3 mm for displacement and 3° for rotations. Three participants of each group have been omitted from the fMRI analysis under this motion criterion. Co-registered images were normalized to the MNI (Montreal Neurological Institute) average template. Statistical analyses were performed on the smoothed images (10 mm isotropic Gaussian kernel), with a high pass filter (128 seconds cutoff period) to remove low frequency artifacts.

Data were entered into a general linear model using an event-related analysis procedure. Stimuli were treated as individual events for analysis and modeled using a canonical HRF (Hemodynamic Response Function). Parameter estimates from contrasts of the canonical HRF in single subject models were entered into random-effects analysis using one-sample *t*-tests across all participants to determine whether activation during a contrast was significant (i.e., parameter estimates were reliably greater than 0). There were three event types: congruent, incongruent, and control. In order to observe the neural correlates of inhibitory control and focused attention, we

compared the incongruent condition to the congruent condition.

For the contrast within each group (pre-treatment atomoxetine, post-treatment atomoxetine, pre-treatment methylphenidate, and post-treatment methylphenidate), all reported areas of activation were significant using $p<.005$ uncorrected at the voxel level in a whole brain analysis as well as $p<.05$ for FWE (familywise error) corrected at the voxel level using *a priori* masks with a cluster size greater than 10 voxels. For the contrasts between groups (pre- vs. post-treatment), all reported areas of activation were significant using $p<.05$ for FWE corrected at the voxel level with a cluster size greater than 10 voxels, with a sphere of 10 mm radius centered on DLPFC, dorsal ACC (dACC), and IFG due to our *a priori* hypothesis (Bush *et al*, 2008; Cubillo *et al*, 2013; Cubillo *et al*, 2014b). In addition, these activations also survived $p<.05$ for FWE or FDR corrected at the voxel level using the cortical area masks provided in the WFU Pick Atlas. A 2 by 2 ANOVA with treatment and visit as factors was conducted to reveal the significant difference of neural changes induced by the two medications. In order to more tightly dissect out the activation linked with congruent and incongruent processing, a sub-analysis was conducted by utilizing the contrast comparing [incongruent-control] and [congruent-control].

We used SPSS to conduct statistical analysis. The descriptive results were displayed as frequency for categorical variables, and mean and SD for continuous variables. Moreover, we computed Pearson's correlations between the differences (pre- vs. post-treatment) of beta values of peak voxels of significant brain regions and the differences (pre- vs. post-treatment) of behavioral performance of the CCPT. All reported results were significant at $p < .05$.

3. Results

3.1 Sample description and medication

There was no significant difference in sex, age, and IQ scores among the atomoxetine, methylphenidate, and TD groups (Table 1). There were no significant group differences in body weight, vital signs, baseline clinical symptoms, and age onset of ADHD. Mean optimal dosage for the atomoxetine and methylphenidate group were 0.75 mg/Kg/day and 0.86 mg/Kg/day, respectively. Throughout the treatment period, the two groups showed no significant difference in most adverse events, except more dizziness and somnolence in the atomoxetine group (Table S1).

3.2 Clinical and behavioral results

Table S2 presents the accuracy and reaction time of the counting Stroop task, response style and perseveration of the CCPT, as well as the clinical performance indicated by the CGI-ADHD-S. A 2 time points (pre-medication, post-medication) by 2 drugs (atomoxetine, methylphenidate) by 3 conditions (incongruent, congruent, control) ANOVA were performed on reaction time and accuracy of the counting Stroop task, separately. A 2 time points by 2 drugs ANOVA were performed on response style and perseveration of the CCPT, and the CGI-ADHD-S respectively.

Analysis on reaction time showed significant main effect of time point ($F(1, 40) = 9.62$, $p = .004$) and condition ($F(2, 80) = 29.25$, $p < .001$). Reaction time was shorter in post-treatment compared to pre-treatment ($t(125) = -4.83$, $p < .001$), and was shorter in the control and congruent conditions compared to the incongruent condition ($t(83) = -7.48$, $p<.001$; $t(83) = -5.63$, $p < .001$, respectively). Moreover, analysis on accuracy showed significant main effect of condition ($F(2, 80) = 11.12$, $p < .001$), with the control

and congruent conditions being more accurate compared to the incongruent condition ($t(83) = 3.34$, $p = .001$; $t(83) = 3.42$, $p = .001$, respectively). Further analyses showed that reaction time across three conditions was significantly reduced after both atomoxetine ($t(65)=2.694$, $p=0.009$) and methylphenidate ($t(59)=4.079$, $p<0.001$) treatment, respectively. Of importance, both groups showed shorter reaction time in incongruent trials after the treatments (atomoxetine, $t(21)=2.241$, p=0.036; methylphenidate, $t(19)=2.646$, $p=0.016$).

Analysis on CGI-ADHD-S showed significant main effect of time point ($F(1,40)=216$, $p<0.001$), with both groups showed reductions of symptomatic severity after atomoxetine ($t(21)=9.97$, $p<0.001$) and methylphenidate ($t(19)=10.98$, $p<0.001$) treatment. The other effects were not significant ($ps > .05$).

3.3 fMRI results

Table 2 presents activation of the brain regions for the incongruent versus congruent condition for the atomoxetine and methylphenidate groups. Compared to the pre-treatment, less activation was found in the left dACC and left DLPFC at the post-treatment in the atomoxetine group (Figure 3). Compared to the pre-treatment, greater activation was found in the left IFG at the post-treatment in the methylphenidate group (Figure 4). Similar findings with the survival of significance of the aforementioned medication-induced neural changes were obtained in the sub-analysis using the more rigorous contrast comparing [incongruent-control] and [congruent-control]. No age effect was found on the activations of these brain regions before and after the treatment. The neural changes induced by the treatment was also not correlated with the age of participants. These three brain regions were observed in the significant treatment by visit interaction effect in further ANOVA analysis (Table 4).

Compared to the TD group, the atomoxetine and methylphenidate groups showed pre-treatment hyper-activation in DLPFC and dACC, but hypo-activation in IFG (Table S3). There was a positive correlation between the differences (between pre- and post-medication) of signal intensity in left dACC and left DLPFC among the participants in the atomoxetine group (Pearson's correlation coefficient = 0.456, p = 0.044). Mean motion, mean rotation, peak motion and peak rotation of all participants during the counting Stroop task are presented on Table S4.

3.4 Correlations between brain activation and behavioral performance

Table 3 and Figure 5 presents the Pearson's correlations between the signal intensity (difference between pre- and post-medication) in brain regions and the CCPT performance. Regarding atomoxetine, there was a positive correlation between dACC/ DLPFC activation and response style of the CCPT, indicating that the more down-regulation of activation in the left dACC and DLPFC, the greater improvement in focused attention. With regard to methylphenidate, there was a negative correlation between IFG activation and degree of perseveration of the CCPT, indicating that the more up-regulation of IFG activation, the greater reduction in perseveration (index of impulsivity).

Table S5 presents the clinical association with these medication-induced neural changes. No significant correlations were found between clinical improvement and the medication-induced activation changes. However, further analyses showed that across pre- and post- medication groups, the CGI-ADHD-S scores were significantly positively correlated with activations in ACC and DLPFC in the atomoxetine group, along with a significant reversed correlation with IFG activation in the methylphenidate group.

4. Discussion

4.1 Summary of findings

As the first head-to-head comparison study utilizing clinically pertinent duration treatment to investigate the differential chronic effects of methylphenidate and atomoxetine on inhibitory control and focused attention with the largest sample size of drug-naïve children with ADHD, in addition to the behavioral improvement in reaction time of the counting Stroop task induced by both medications, we found that atomoxetine down-regulated activation in left dACC and DLPFC, which was associated with the improvement in focused attention as indicated by response style of the CCPT, while methylphenidate up-regulated left IFG activation, which was associated with the reduction in impulsivity as indicated by perseveration of the CCPT.

4.2 Down-regulation of activation in DLPFC and ACC by atomoxetine

A conceptual relation between behavioral inhibition and focused attention has been long established (Neill *et al*, 1995). Our findings that down-regulation of dACC and DLPFC activation induced by atomoxetine was associated with improved focused attention gain support from a recent head-to-head comparison study on executive functions in adults with ADHD, reporting the drug-specific improvement in attention after treatment with atomoxetine for 8-10 weeks (Ni *et al*, 2013a). Functional changes in DLPFC supported by the behavioral improvement further underpin the idea that this region may be regarded as drug-specific target of atomoxetine (Cubillo *et al*, 2013). The prefrontal cortex has been implicated in attentional processes, working memory, and inhibition (Fassbender and Schweitzer, 2006). Structural as well as functional alternations in this region have been reported in ADHD (Fassbender *et al*, 2006).

Single-dose administration of atomoxetine up-regulated prefrontal activation of both boys with ADHD (Cubillo *et al*, 2013; Cubillo *et al*, 2014b) and healthy adults (Chamberlain *et al*, 2009; Graf *et al*, 2011), in line with the acute effect of atomoxetine in increasing prefrontal extracellular dopamine and norepinephrine in animal models (Bymaster *et al*, 2002; Swanson *et al*, 2006). Nevertheless, the single-dose effect may not fully explain the therapeutic mechanism leading to clinical improvement (Koda *et al*, 2010; Schulz *et al*, 2012) because of several differential effects between chronic and acute administration of atomoxetine (Fumagalli *et al*, 2010; Koda *et al*, 2010; Sun *et al*, 2012). For example, using dosage equivalent to the clinical treatment (i.e., 1 mg/kg), the increase of prefrontal norepinephrine induced by atomoxetine was down-regulated by chronic administration (Koda *et al*, 2010). This finding is in agreement with the observation that chronic atomoxetine exposure increases norepinephrine transporter mRNA, while decreasing markers of synaptic plasticity (Sun *et al*, 2012). Down-regulation of DLPFC activation observed in our present study extends the findings from the rodent model to human beings. In contrast, up-regulation of right DLPFC activation has been reported among adults with ADHD after 6-week treatment of atomoxetine (Bush *et al*, 2013). Different ages of participants, dosage and duration of the treatment, and cognitive tasks selected may contribute to this discrepancy. Considering the limited neuroimaging studies on atomoxetine, further investigation is needed to clarify the chronic effect between children and adults with ADHD, as well as treatments with different dosages given the dose-response relationship of catecholaminergic signaling in prefrontal cortex (e.g., Marquand *et al* (2011)).

The dACC has been implicated in the suppression of inappropriate response and plays an essential role during the counting Stroop task (Bush *et al*, 1999; Bush *et al*, 1998). The down-regulation of dACC activation observed in this study was in line with

the ACC deactivation in boys with ADHD after single-dose administration of atomoxetine (Cubillo *et al*, 2013). Hyperactivation in dACC of children with ADHD relative to comparison participants was reported in a comprehensive meta-analysis of fMRI studies (Cortese *et al*, 2012). In particular, increased dACC activation was correlated with inhibition failure (Hester *et al*, 2004; Schulz *et al*, 2004). Parallel findings observed in a PET study indicated greater recruitment of dACC for impaired decision making performance in adults with ADHD (Ernst *et al*, 2003). The present finding of positive correlations with dACC and DLPFC was in accordance with the cortico-cortical connections between these brain regions found in both structural and functional studies (Paus, 2001). These functionally connected regions support attentional reorienting to salient stimuli (Kucyi *et al*, 2012). Since suppression of this network is needed to screen out distracting salient stimuli, hyperactivation in dACC and DLPFC may underpin the distractibility of ADHD (Cortese *et al*, 2012). Taken together, our findings suggest that atomoxetine may promote behavioral improvement by successful suppression of salience network.

Several neurocomputational models have been proposed outlining how norepinephrine activity of locus coeruleus (LC) response to salient stimuli and further organize adaptive behaviors (Bouret and Sara, 2005; Dayan and Yu, 2006). Strength of this salience network was reduced after inhibition of beta-adrenergic receptor (Hermans *et al*, 2011). Extending the adaptive gain theory of LC-NE function (Aston-Jones and Cohen, 2005a, b), Corbetta *et al* (2008) proposed the functional relationship between the decreased tonic LC activity, which promotes the filtering of distractors, and the deactivation of the brain regions that response to salient stimuli. Added to the observation that the most prominent cortical projections to LC were innervated by ACC (Aston-Jones *et al*, 2005b), the reciprocal functional interaction confirmed by the

behavioral results was established between these two regions (Gompf *et al*, 2010). Therefore, considering the fact that atomoxetine selectively blocks norepinephrine transporter, which located the most in LC, down-regulation of both dACC and DLPFC activation observed in the current study may be the indirect chronic therapeutic mechanism induced by atomoxetine through the pharmacologic action in LC.

4.3 Up-regulation of activation in IFG by methylphenidate

The observed up-regulation of the left IFG activation along with decreasing impulsivity after treatment with OROS methylphenidate is in accordance with previous studies. As the main indicator of inhibitory control, dysfunction in the IFG is one of the most consistent findings of fMRI studies in ADHD (Cortese *et al*, 2012). A single dose of methylphenidate consistently up-regulated IFG activation in ADHD across a variety of task paradigms designed to assess inhibitory control (Cubillo *et al*, 2014b; Rubia *et al*, 2011). These observations were further supported by structural (Shaw *et al*, 2009) and functional (Pliszka *et al*, 2006) neuroimaging studies comparing medication-naïve children (Pliszka *et al*, 2006) and adolescents (Shaw *et al*, 2009) to those with a medication history. In a prospective study on the effect of 6-week methylphenidate treatment in adults with ADHD, Bush *et al* (2008) also found up-regulation of the left IFG. These findings are partially supported by the evidence in animal studies, in which chronic methylphenidate treatment did not alter its acute effect in prefrontal cortex. Methylphenidate-induced increase of the prefrontal norepinephrine and dopamine was not affected by chronic treatment in microdialysis study using rodent models (Koda *et al*, 2010), while PET studies (Gill *et al*, 2012) on nonhuman primates showed that long-term methylphenidate administration did not cause any long-term alteration on the

dopamine system. Taken together, IFG activation may be a reliable indicator for both acute and chronic treatment response of methylphenidate.

4.4 Limitations

One of the limitations of this study might be the relatively large age range (7-17 years old) of participants recruited, although it would not affect the within-subject analyses and age-matched group design. Since brain maturation and development may introduce variability into the medication effect (Schweren *et al*, 2013), further studies with participants of a narrower age range are warranted. Absence of placebo arm may be another limitation of this present study. However, it is ethically questionable to withhold medication from children with ADHD who have been indicated for pharmacotherapy. Though an impressive sample size was utilized in our study, enabling the significant findings on medication-induced neural changes and associated behavioral improvement in CCPT, no significant correlation between activation changes and clinical improvement was observed. The sample size of about twenty participants in each group may not be adequate considering the maximum score range of seven points designed in the CGI-ADHD-S.

4.5 Strengths and novelties

Despite above-mentioned limitations, the unique focus of this present study is the head-to-head comparison on the chronic effects between atomoxetine and methylphenidate, together with several innovative approaches constituting its strength: a randomized clinical trial rather than naturalistic design, and the recruitment of medication-naïve children with ADHD, and avoiding the potential confounding effects of medication history. In addition, we incorporated a variety of clinic-relevant study

design elements: combination of neuroimaging and neuropsychological assessments, enabling exploration of behavioral improvement accompanied by the neural changes; head-to-head comparison between the two main medications for ADHD, instead of placebo, providing valuable guidance towards therapeutic decisions; and a long-term treatment (up to 12 weeks) rather than a single dose study design.

There are several reasons for the long-term treatment study design. First, ADHD is a neurodevelopmental disorder with a persistence rate of 50-65% at adulthood (Faraone *et al*, 2006), and long-term pharmacotherapy is proven beneficial and may be necessary. Second, despite the acute effect of methylphenidate, clinical efficacy of both medications does not maximally differentiate from placebo until weeks of treatment (Biederman *et al*, 2006; Montoya *et al*, 2009). Third, given chronic pharmacotherapy in children with ADHD at the critical period of major developmental brain changes, particularly the prefrontal cortex, a long-term study could provide valuable insight into the ongoing medication effect on the developing brain (Fumagalli *et al*, 2010; Shaw *et al*, 2009) .

4.6 Conclusions

In conclusion, the current findings demonstrated that chronic treatment with atomoxetine improved focused attention by down-regulating cingulo-frontal activation, while chronic treatment with methylphenidate reduced impulsivity by up-regulating left inferior frontal activation. These differential changes in brain activation were associated with improvement of inhibitory controls and focused attention. Taken together, the present study provides strong evidence to support the differential functional brain changes underlying behavioral improvement induced by chronic treatment with atomoxetine and methylphenidate.

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Figures

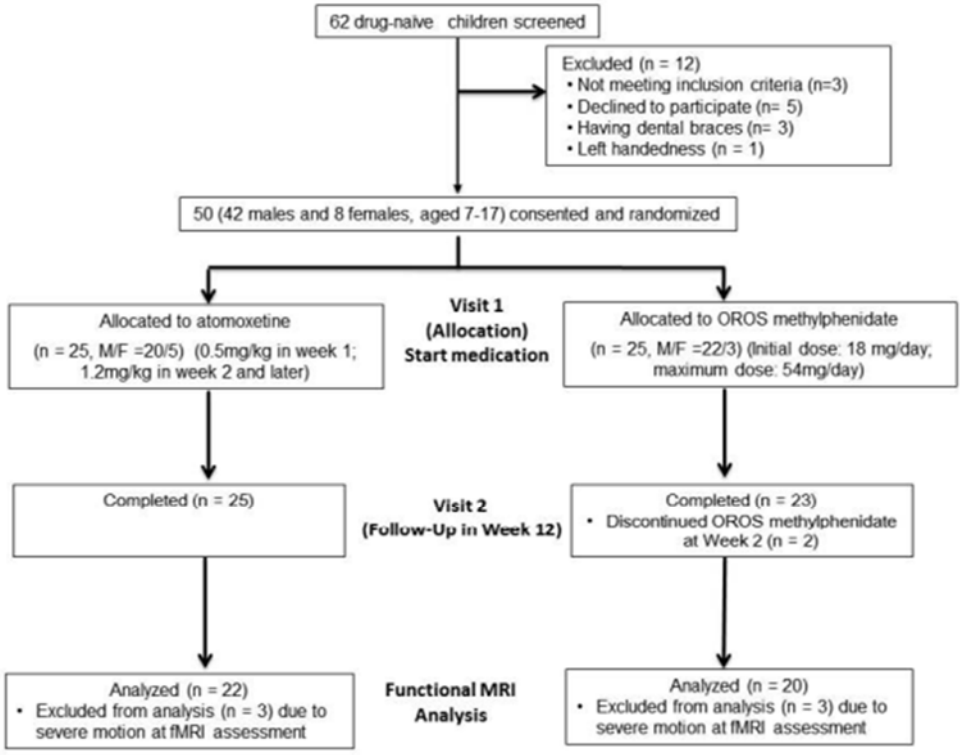

Figure 1: Flow diagram of the randomization procedure and outcome of all recruited subjects. M, male; F, female.

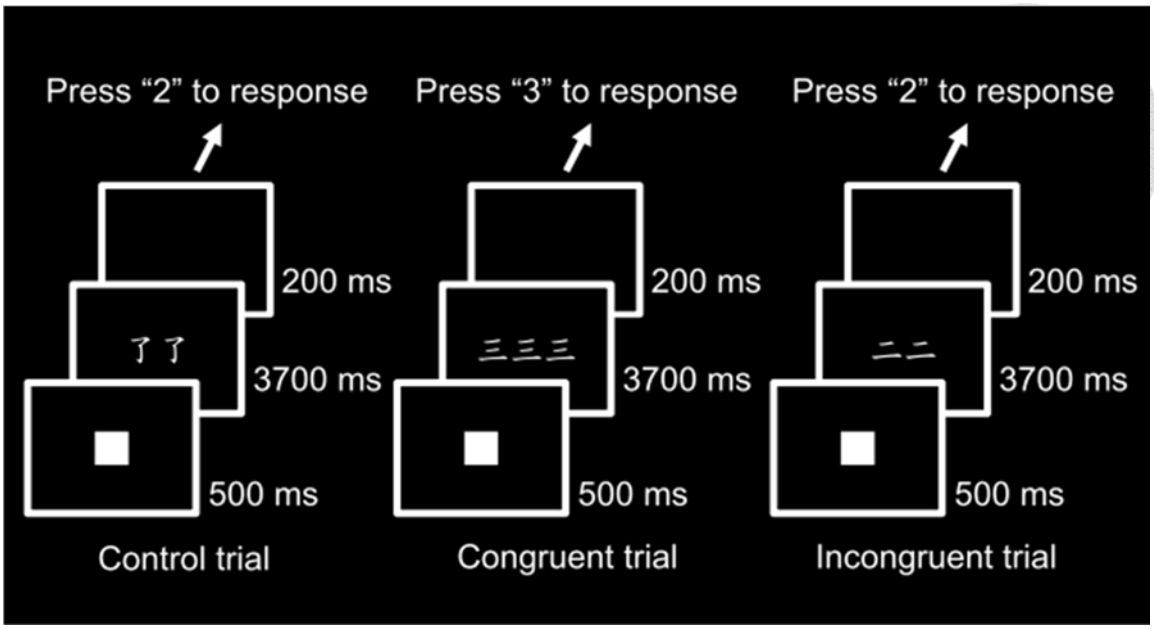

Figure 2: The counting Stroop task in Chinese. Experimental stimuli were divided into the congruent, incongruent, and control conditions. In the ‘‘congruent’’ condition, the number of words (i.e., one) was consistent with the meaning of the word (i.e., one). In the ‘‘incongruent’’ condition, the number of words (i.e., three) was inconsistent with the meaning of the word (i.e., four). In the ‘‘control’’ condition, the Chinese words did not give any clue to number.

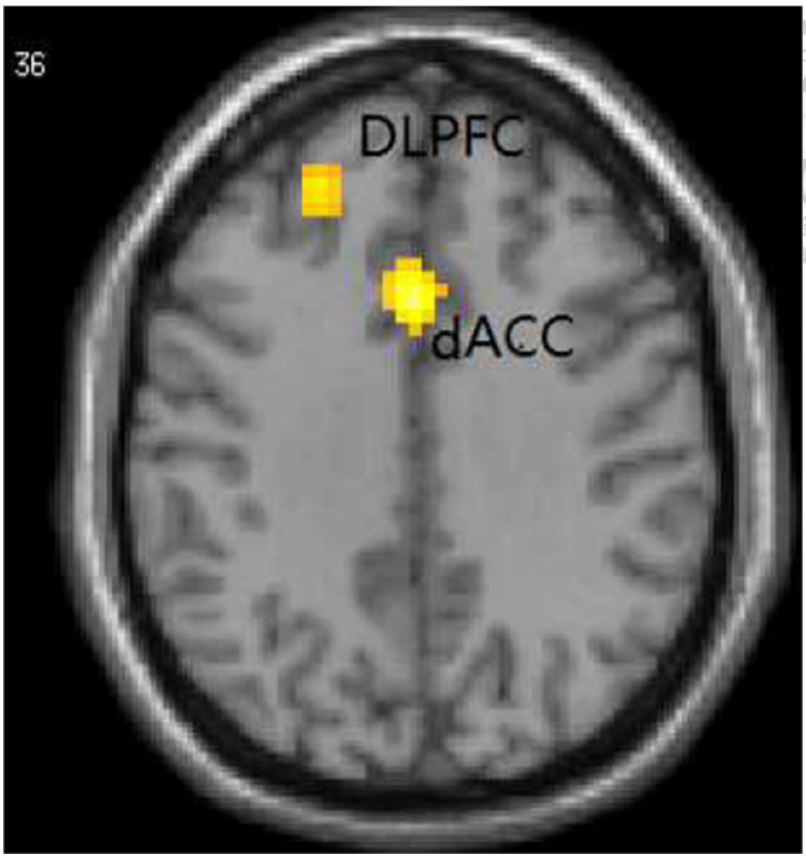

Figure 3: Greater activation in left dorsal anterior cingulate cortex (dACC) and dorsolateral prefrontal cortex (DLPFC) from pre-treatment to post-treatment with atomoxetine in children with ADHD.

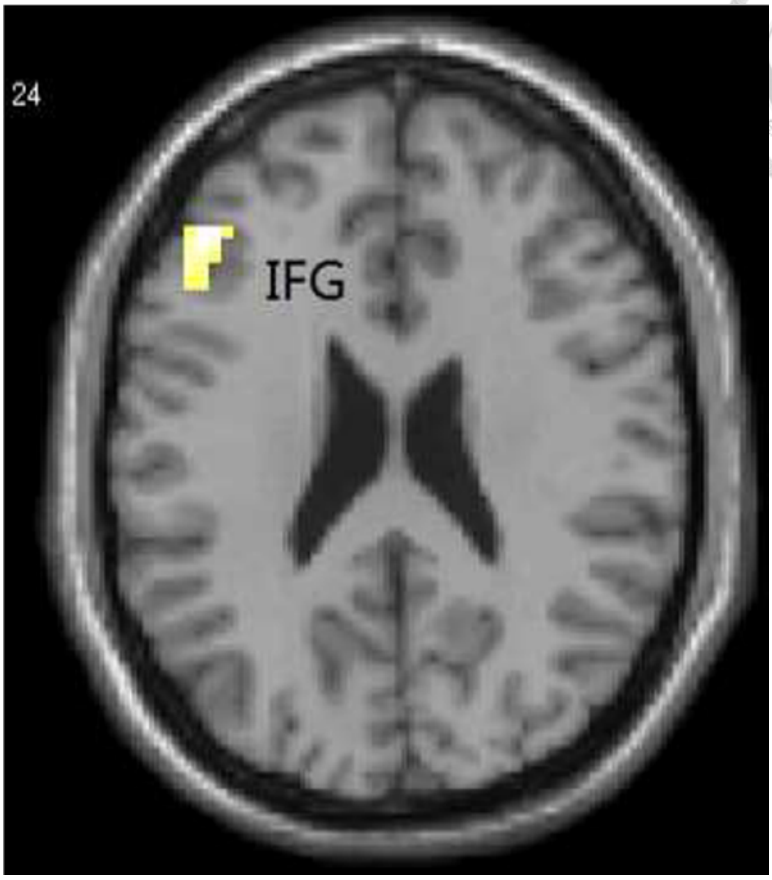

Figure 4: Greater activation in left inferior frontal gyrus (IFG) from pre-treatment to post-treatment with methylphenidate in children with ADHD.

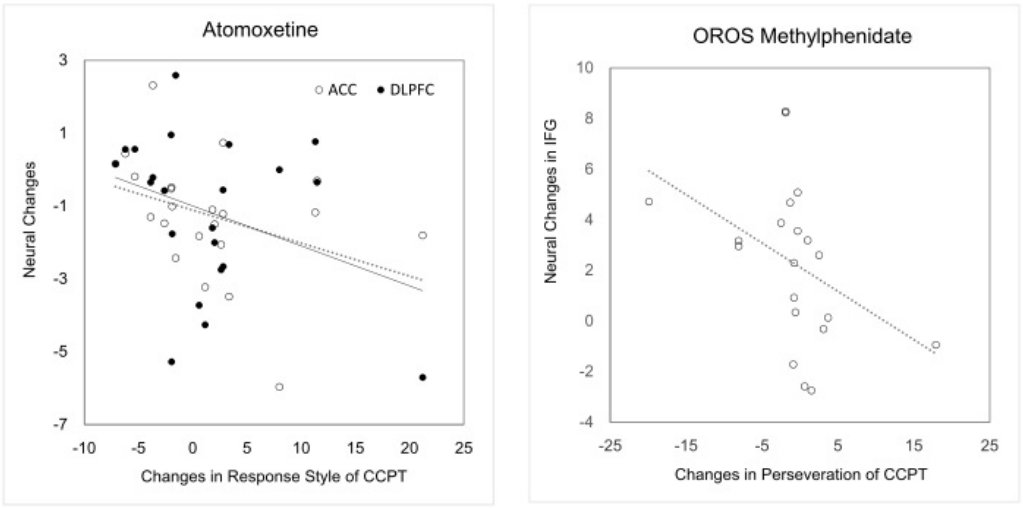

Figure 5: Correlations between neural changes (post-treatment versus pre-treatment) and behavioral changes (post-treatment versus pre-treatment) in CCPT.

Tables

Table 1. Baseline Sample Characteristics

	Atomoxetine (n = 22)	**OROS Methylphenidate (n = 20)**	**Typically Developing (n = 20)**	**Statistics**	***p* value**
Sex (Male/Female)	17/5	17/3	16/4	$\chi^2(2) = 0.41$	0.82
Mean Age (Mean ± S.D.)	10.55 ± 2.20	10.45 ± 2.26	12.05±2.70	F(2,59) = 2.85	0.07
Age Range	7-17	7-14	8-17		
Full-scale IQ (Mean ± S.D.)	107.6 ± 10.7	109.5 ± 13.5	106.5±11.1	F(2,59) = 0.33	0.72
Clinical Symptoms (Mean ± S.D.)					
Inattention	7.84 ± 1.21	7.74 ± 1.56		*t*(40) = 0.241	0.81
Hyperactivity	3.32 ± 1.84	3.16 ± 2.06		*t*(40) = 0.263	0.79
Impulsivity	1.57 ± 1.20	1.68 ± 0.96		*t*(40) = 0.338	0.74
Age Onset (Mean ± S.D.)	5.07 ± 2.20	5.42 ± 2.74		*t*(40) = 0.458	0.65

Optimal Dosage, mg (Mean ± S.D.)	31.83 ± 10.42	28.79 ± 14.89		
Optimal Dosage, mg/Kg (Mean ± S.D.)	0.75 ± 0.33	0.86 ± 0.48		
Body Weight, Kg (Mean ± S.D.)	42.47 ± 11.54	40.39 ± 14.56	$t(40) = 0.496$	0.62
Vital Signs				
Systolic Pressure	104.9 ± 10.1	104.3 ± 8.9	$t(40) = 0.175$	0.86
Diastolic Pressure	67.8 ± 7.2	66.1 ± 10.3	$t(40) = 0.599$	0.55
Heart Rate	75.50 ± 13.16	82.11 ± 10.98	$t(40) = 1.697$	0.10

Note. ADHD, Attention Deficit/Hyperactivity Disorder; S.D., Standard Deviation; OROS, Osmotic Controlled Released Oral Delivery System.

Table 2. Greater Activation for the Incongruent Condition Compared to the Congruent Condition for the ADHD Treated with Atomoxetine and ADHD Treated with Methylphenidate, and Direct Comparison between the Pre-treatment and Post-treatment for the Two Treatment groups.

Cortical regions	H	BA	Voxels	Z test	MNI coordinates		
					X	Y	Z
Atomoxetine							
pre-treatment							
Precentral gyrus	R	6	305	3.65	30	-15	60
Superior parietal lobe	R	7	98	3.63	12	-57	60
	L	7	101	2.95	-18	-51	60
Dorsal anterior cingulate cortex [a]	L	32	46	3.62	-3	9	42
	R	32	69	3.37	3	12	42
Insula	L	13	169	3.00	-39	15	-3
Middle temporal gyrus	R	19	11	2.64	48	-72	12
Dorsolateral prefrontal cortex [a]	L	9	10	2.33	-24	39	36
post-treatment							
Precentral gyrus	R	4	74	3.74	30	-27	54
Insula	L	13	34	3.53	-30	12	15
	R	13	16	3.11	33	12	0
pre- > post-treatment							
Dorsal anterior cingulate cortex		32	50	3.20	0	15	39
Dorsolateral prefrontal cortex	L	9	31	2.73	-21	42	36
post- > pre-treatment							
None							

OROS Methylphenidate							
pre-treatment							
Superior temporal gyrus	L	22	138	4.02	-63	-48	15
Postcentral gyrus	R	3	54	2.88	36	-39	66
post-treatment							
Medial frontal gyrus	R	8	67	3.39	3	30	54
Middle frontal gyrus	L	9	34	2.99	-36	21	42
Postcentral gyrus	R	3	30	2.87	42	-24	48
Inferior frontal gyrus [a]	L	47	10	2.85	-51	15	-6
	L	45	10	2.38	-39	21	27
Superior parietal lobe	R	7	23	2.69	36	-69	51
pre- > post-treatment							
None							
post- > pre-treatment							
Inferior frontal gyrus	L	45	52	2.95	-45	33	24

Note: H, hemisphere; L, left; R, right; BA, Brodmann's area; Voxels, only clusters greater than 10 are presented, for contrast within each group, number of voxels in cluster at $p < .005$ uncorrected and [a] number of voxels in cluster at $p < .05$ for FWE (familywise error) corrected with the use of *a priori* masks; for contrast between groups, number of voxels in cluster at $p < .05$ for FWE corrected with the use of the masks. Coordinates of activation peak(s) within a region based on a z test are given in the MNI stereotactic space (x, y, z).

Table 3. Correlations between the Activation Changes with the Performance Changes of the Conners' Continuous Performance Test.

Note: ADHD, attention-deficit/hyperactivity disorder.

ADHD treated with atomoxetine		
Dorsal anterior cingulate cortex	**Correlations Coefficient**	***p* value**
Response style	-0.479	**0.044***
Dorsolateral prefrontal cortex		
Response style	-0.454	**0.034***
ADHD treated with OROS methylphenidate		
Inferior frontal gyrus	*R*	*p* value
Perseveration	-0.472	**0.048***

Table 4. Brain Regions Showing Treatment by Visit Interactions, Main Effect of Treatment, and Main Effect of Visit on Activation for the Participants.

Cortical regions	H	BA	Voxels	F test	Z test	MNI coordinates		
						X	Y	Z
Treatment by Visit Interactions								
Dorsolateral prefrontal cortex[a]	L	9	67	12.34	3.21	-27	45	39
Precentral gyrus	L	6	125	11.39	3.07	-33	-18	66
Middle frontal gyrus	R	6	30	11.19	3.05	24	21	60
Superior parietal lobe	L	7	185	11.00	3.02	-21	-69	60
Superior temporal gyrus	L	22	16	10.63	2.96	-54	12	-3
Dorsal anterior cingulate gyrus[a]	L	32	8	7.75	2.49	0	21	39
Inferior frontal gyrus[a]	L	45/46	6	7.74	2.49	-45	33	26
Main Effects of Treatment								
Inferior frontal gyrus	L	45	195	11.55	3.10	-57	39	3
Medial frontal gyrus	R	6	84	2.98	2.98	9	33	60
Supramarginal gyrus	L	40	15	8.49	2.62	-60	-48	30
Main Effects of Visit								
Lentiform nucleus	R		34	11.30	3.06	15	0	-3
	L		19	8.56	2.63	-12	0	3
Supplementary motor area	L	6	32	11.23	3.05	-9	6	66

Note: H, hemisphere; L, left; R, right; BA, Brodmann's area; Voxels, only clusters greater than 5 are presented with voxels in cluster at $p < .01$ uncorrected. [a] Activations were significant using $p \leq .05$ for FWE (family-wise error) or FDR (false discovery rate) corrected with the use of *a priori* masks within a 10mm sphere in 3 regions of interest as well as the cortical area masks.

Coordinates of activation peak(s) within a region based on a z test are given in the MNI stereotactic space (x, y, z).

Supplementary Tables

Table S1. Adverse Events for Children with ADHD Who Were Treated with Atomoxetine and OROS Methylphenidate

	Atomoxetine (n=22)	OROS Methylphenidate (n=20)	*Fish's Exact p* value
Decreased appetite	8	9	0.751
Vomiting	3	1	0.605
Abdomen-ache	4	2	0.661
Insomnia	2	1	1.000
Somnolence	9	0	0.001*
Dizziness	6	0	0.020*
Stomachaches	1	1	1.000
Headaches	5	3	0.695
Other	0	4	0.047*

Note: ADHD, attention-deficit/hyperactivity disorder. Fisher's exact 2-tailed p values were computed because most of the numbers of sample size for each cell were below 5.

Table S2. Comparison of Accuracy and Reaction Time of the Counting Stroop Task in Three Conditions for Children with ADHD Treated with Atomoxetine and Children with ADHD Treated with OROS Methylphenidate.

	Atomoxetine		**OROS Methylphenidate**	
Variable	**Pre Treatment**	**Post Treatment**	**Pre Treatment**	**Post Treatment**
Counting Stroop task				
Accuracy (%)				
Control	95±6	94±7	93±7	92±10
Incongruent	92±8	93±9	90±7	89±13
Congruent	94±9	95±10	95±6	95±8
Reaction Time (ms)				
Control	1013±219	967±195	1027±271	921±191
Incongruent	1114±241	1034±219	1145±318	1012±192
Congruent	1026±246	983±210	1061±252	960±224
Continuous Performance Test				
Response Style	0.553±0.292	0.63±0.476	0.805±0.489	0.61±0.457
Perseveration	10.64±10.71	10.18±12.81	16.60±19.20	12.95±15.23

Table S3. Greater Activation for the Incongruent Condition Compared to the Congruent Condition for the Direct Comparison between Typically Developing Group and the Two Treatment Groups Before Receiving Treatment.

Cortical regions	H	BA	Voxels	Z test	MNI coordinates		
					X	Y	Z
Atomoxetine							
pre-treatment > typically developing							
Superior parietal lobe	R	7	114	3.30	18	-48	63
	L	7	186	3.11	-21	-45	60
Precentral gyrus	L	4	45	2.68	-27	-24	63
Dorsal anterior cingulate cortex	L	32	42	2.33	-3	6	45
Dorsolateral prefrontal cortex	L	9	11	2.32	-27	39	39
typically developing > pre-treatment							
Medial frontal gyrus	R	6	57	3.29	6	33	60
Inferior frontal gyrus	R	47	11	2.51	45	42	0
Methylphenidate							
pre-treatment > typically developing							
Postcentral gyrus	R	5	16	2.67	27	-45	63
typically developing > pre-treatment							
Superior parietal lobe	L	7	12	2.99	-39	-66	57
Inferior frontal gyrus	L	45	34	2.85	-42	36	21
Medial frontal gyrus	R	10	17	2.71	18	57	6

Note: H, hemisphere; L, left; R, right; BA, Brodmann's area; Voxels, only clusters greater than 10 are presented, number of voxels in cluster at $p < .01$ uncorrected. Coordinates of activation peak(s) within a region based on a z test are given in the MNI stereotactic space (x, y, z).

Table S4. Mean Motion, Mean Rotation, Peak Motion and Peak Rotation of All Participants During the Counting Stroop Task.

	Atomoxetine		Methylphenidate	
Variable	**Pre-Treatment**	**Post-Treatment**	**Pre-Treatment**	**Post-Treatment**
Mean motion	0.116±0.060	0.113±0.064	0.133±0.068	0.101±0.034
Mean rotation	0.001±0.000	0.001±0.001	0.001±0.001	0.001±0.001
Peak motion	0.601±0.332	0.768±0.619	0.774±0.409	0.605±0.336
Peak rotation	0.007±0.003	0.011±0.135	0.011±0.005	0.010±0.008

Table S5. Clinical Association with Medication-induced Neuronal Changes. (a) Correlations between the Activation Changes with the Reduction in Symptomatic Severity on CGI-ADHD-S, (b) Correlations between the Brain Activations and Symptomatic Severity on CGI-ADHD-S across pre-and post- treatments.

Activation Changes[a]	**Reduction in Symptomatic Severity**[a]	
ADHD treated with atomoxetine	**Correlations Coefficient**	***p* value**
Dorsal anterior cingulate cortex	-0.263	0.277
Dorsolateral prefrontal cortex	-0.078	0.780
ADHD treated with methylphenidate		
Inferior frontal gyrus	0.193	0.457
Brain Activations[b]	**Symptomatic Severity**[b]	
ADHD treated with atomoxetine	**Correlations Coefficient**	***p* value**
Dorsal anterior cingulate cortex	0.343	0.038*
Dorsolateral prefrontal cortex	0.428	0.008*
ADHD treated with methylphenidate		
Inferior frontal gyrus	-0.358	0.025*

Note: [a] Both activation changes and reduction in symptomatic reduction for the post-treatment group compared to the pre-treatment group.

Table S6. Greater Activation Observed in the Contrast "incongruent-control' Compared to "congruent-control" for the Direct Comparison between the Pre-treatment and Post-treatment for the Two Treatment groups.

Cortical regions	H	BA	Voxels	Z test	MNI coordinates		
					X	Y	Z
Atomoxetine							
pre-treatment							
Postcentral gyrus	R	6	337	3.74	45	-24	57
Dorsal anterior cingulate cortex	L	32	76	3.23	0	12	42
Superior parietal lobe	R	7	73	3.08	15	-54	63
	L	7	59	2.94	-18	-57	57
Insula	L	13	34	2.63	-45	9	0
Dorsolateral prefrontal cortex [a]	L	9	11	1.97	-24	39	39
post-treatment							
Precentral gyrus	R	4	69	2.97	27	-27	57
Insula	L	13	14	2.92	-30	12	15
	R	13	11	2.74	33	12	3
pre- > post-treatment							
Dorsal anterior cingulate cortex		32	159	3.57	0	15	39
Dorsolateral prefrontal cortex[a]	L	9	10	2.44	-21	42	36
post- > pre-treatment							
None							
Methylphenidate							
pre-treatment							
Superior temporal gyrus	R	28	38	3.58	36	18	-27

	L	22	18	2.89	-63	-48	15
Postcentral gyrus	R	3	31	2.81	36	-36	66
post-treatment							
Superior temporal gyrus	R	22	25	3.51	63	-6	6
	R	42	18	3.23	66	-33	18
Medial frontal gyrus	R	8	50	3.30	9	24	51
Middle frontal gyrus	L	9	50	3.45	-33	18	42
Postcentral gyrus	L	43	51	3.02	-66	-21	18
Precentral gyrus	R	4	17	2.79	36	-24	51
Inferior frontal gyrus[a]	L	45	13	2.83	-36	18	36
	L	47	10	2.49	-54	6	6
pre- > post-treatment							
None							
post- > pre-treatment							
Inferior frontal gyrus[a]	L	45/46	12	2.53	-45	33	21

Note: H, hemisphere; L, left; R, right; BA, Brodmann's area; Voxels, only clusters greater than 10 are presented, for contrast within each group, number of voxels in cluster at $p < .01$ uncorrected and [a] number of voxels in cluster at $p < .05$ for FWE (familywise error) corrected with the use of *a priori* masks. Coordinates of activation peak(s) within a region based on a z test are given in the MNI stereotactic space (x, y, z).