European Child & Adolescent Psychiatry
https://doi.org/10.1007/s00787-019-01434-1

ORIGINAL CONTRIBUTION

Annual variation in attentional response after methylphenidate treatment

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Received: 12 June 2019 / Accepted: 28 October 2019

Abstract

Prevalence rates of attention-deficit/hyperactivity disorder (ADHD) differ with geographical areas varying in sunlight intensity. Sun- or daylight reaching the retina establishes entrainment of the circadian clock to daylight. Changes herein, hence, alterations in clock alignment, could be reflected indirectly in inattention via sleep duration. We here studied (1) annual variation in inattention at treatment initiation; (2) annual variation in response to ADHD treatment [methylphenidate (MPH)] by day of treatment initiation; and (3) dose dependence. We predicted least baseline inattention during a period of high sunlight intensity implying more room for improvement (i.e., a better treatment response) when sunlight intensity is low. These hypotheses were not confirmed. High-dose treated patients, however, had significantly better attention after treatment than low-dosed treated patients, only when treated in the period from winter to summer solstice. Change in solar irradiance (SI) during low-dosed treatment period was negatively related to attentional improvement. The above described findings were primarily found in inattention ratings and replicated in omission errors on a continuous performance task. Daylight and inattention have been proposed to be related via mediation of the circadian system. One mechanism of MPH may be to enhance sensitivity to the diurnal entrainment to sunlight and the question can be raised whether appropriate lighting could potentiate the effects of stimulants.

Keywords Methylphenidate · ADHD · Sunlight · Inattention · Annual variation

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s00787-019-01434-1) contains supplementary material, which is available to authorized users.

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Published online: 20 November 2019

Introduction

Prevalence rates of attention-deficit/hyperactivity disorder (ADHD) are relatively low in geographical areas characterized by high sunlight intensity [1]. When sunlight reaches the retina, it provides the internal circadian clock with information about the time of day, thereby leading to daylight entrainment [2]. Dawn is most predominantly linked to daylight entrainment [3] and especially changes in daylength are thought to influence the circadian system [4]. Potential alterations in clock alignment could be reflected indirectly in inattention via sleep duration [5], and even modest misalignment of the clock from sleep/wake behavior can result in poorer quality of sleep [6]. Patients with ADHD may respond differently to clock misalignment, since there are indications that the response to light is altered in these people. Evidence for this mostly comes from the robust finding that the majority of patients with ADHD suffer from a delayed circadian phase associated with late sleep onsets [7], but also from higher than expected levels of photophobia found in this group [8]. Furthermore, there are indications that ADHD treatment [methylphenidate (MPH)] has impact on the circadian processes, although the exact nature is not clear yet [7]. We here studied (1) annual variation in inattention at treatment initiation; (2) annual variation in response to MPH by day of treatment initiation; and (3) dose dependence of these effects. The correlation between inattention before and after treatment with sunlight intensity and its change following treatment initiation were also studied. We addressed these questions using data from a phase-IV, multisite, international, open-label effectiveness trial in which ADHD patients received MPH for 6 weeks. Inattention ratings were defined as the primary outcome variable, while omission errors on a continuous performance task (CPT) were secondary. We predicted least baseline inattention during a period of high sunlight intensity implying more room for improvement when sunlight intensity is low. In addition, we studied dose dependence of the effects.

Methods

This study included 336 ADHD patients (6–17 years old; 11.9 ± 3.3 years; $N = 245$ males) from the International Study to Predict Optimized Treatment in ADHD (iSPOT-A). Full-study protocol details have been published elsewhere [9]. Patients were recruited in Europe, the USA, and Australia between September 2009 and April 2012. In summary, a primary clinical diagnosis of ADHD was confirmed at baseline. Participants were unmedicated for 7 days prior to baseline testing (i.e., naïve or washed out). They were submitted to MPH treatment for 6 weeks and were required to have a minimum duration of MPH treatment for 4 weeks; while refraining from other ADHD treatments, including other stimulants, non-stimulant ADHD drugs, and non-pharmacological ADHD therapies during the 6 weeks. Participants were assessed at baseline and week 6.

Analysis

Inattention

The primary outcome was defined as inattention using (1) the inattentive subscale of the ADHD-Rating Scale (RS); and (2) omission errors on the continuous performance task (CPT inattention), described in the supplement. A non-significant low correlation between the two measures was found ($r = 0.167$, $p = 0.070$). In the supplement, analyses are reported for the hyperactivity/impulsivity subscale of the ADHD-RS and commission errors on the CPT as well.

Annual variation

We studied inattention by day of treatment initiation, adjusted towards seasonality of the northern hemisphere. Annual patterns in inattention at baseline, endpoint, and in treatment response (endpoint–baseline) were studied. We separately studied the periods centered around and between solstices, where the summer solstice was day 172 for the northern hemisphere and day 355 for the southern hemisphere, and winter solstice day 355 and 172, respectively. A curve fitting approach, as described in the supplement, was applied to test a season-dependent pattern in the treatment response.

Sunlight exposure

For each site, solar irradiation (SI) was calculated per month using "*meteonorm 7*" (http://www.meteonorm.com/en/downloads). Interpolation of data from weather stations surrounding that site was used (supplement, Table S1), resulting in a monthly global solar irradiation (Gh kWh/m^2) from five interpolated locations (SI), and the difference between SI during the month of treatment initiation and the subsequent month [SI change (SIC)]. The correlation between baseline inattention and treatment response with sunlight intensity (SI) and its change following treatment initiation (SIC) were studied.

Statistics

Statistical tests were employed using IBM SPSS Statistics for Macintosh 25.0. Significance level was set at $p < 0.05$.

Distributions of the data were examined and informed the decision to test relationships parametrically or non-parametrically. Median-split analyses were run on dosage and low- and high-dosage groups were compared on medication response. To investigate whether the observed effects were linear or non-linear curve fitting was applied (see supplement).

Results

This study included 336 ADHD patients. Of these, 278 patients adhered to the protocol. Sites needed to have contributed $N \geq 10$ to the data set to be included in the analyses. This led to the exclusion of data from Asheville (NC, USA), leaving a sample of $N = 275$. To run median-split analyses, data from an additional seven patients were excluded, because dosage was unknown for these patients. Final analyses were conducted on a sample of $N = 268$. The median-split dosage groups did not significantly differ on baseline inattention, age, or sex. The below median (low) dosage group received a mean dosage of 0.28 ± 0.10 mg per kg per day, while the above median (high) dosage group received 0.76 ± 0.32 mg per kg per day.

Annual variation

Annual variation in inattention at baseline and endpoint is visualized in Fig 1. A Loess fit suggested annual variation emerging after treatment for the low-dosed group, lacking at treatment initiation (Fig 1a). For the high-dosage group, no annual variation was observed (Fig 1b). We compared the low- and high-dosage group after treatment for the period between winter and summer solstice (winter–summer) and between summer and winter solstice (summer–winter). For winter–summer, high-dosed patients had significantly better attention than low-dosed patients ($U = 2102$, $p = 0.042$). For summer–winter, however, response was independent of dosage ($U = 1713$, $p = 0.612$). Testing CPT inattention showed significantly fewer omission errors in the high than in the low-dosed group in winter–summer ($U = 691.5$, $p = 0.011$), but response was independent of dosage in summer–winter ($U = 787.5$, $p = 0.411$). Comparing the low- and high-dosage groups for the periods around the solstices (summer: day 81–264, winter: day 264–81) did not result in significant differences between groups for either outcome measure. Apparent from the data (Fig 1b), the above-demonstrated differences vary largely within the periods (rather than between) when selecting days around solstices.

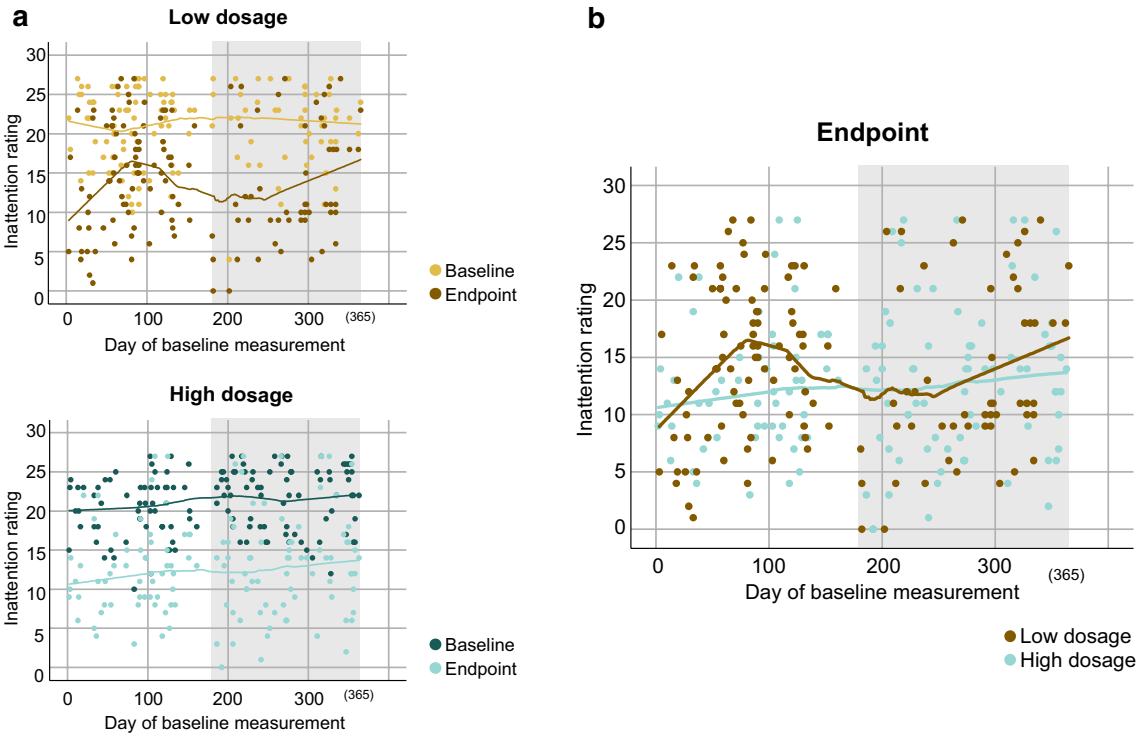

Fig. 1 Inattention ratings per day of treament initiation. The white shaded area indicates the period between winter and summer solstice, and the gray shaded area indicates the period between summer and winter solstice, adjusted towards seasonality of the northern hemisphere. Inattention ratings are presented for **a** baseline and endpoint, median split on low dosage (top panel) and high dosage (bottom panel), and for **b** low and high dosages at endpoint. *NB* a lower value implies a better outcome

A curve fitting approach favored a sinusoidal fit of 365 days over a straight horizontal line for the low-dosage group, but not for the high-dosage group (see supplement for details of this analysis).

Sunlight exposure

SI and SIC were uncorrelated with baseline inattention. Circannual variation in treatment response for the low-dosage group shows similarity with circannual variation in SIC (Fig 2a). Hence, SIC positively correlated with treatment response in inattention, albeit only in the low-dosage group ($r = 0.218$, $p = 0.011$, $R^2 = 0.05$). These results were replicated for CPT inattention (low dosage: $r = 0.246$, $p = 0.020$, $R^2 = 0.06$). The positive correlations found indicate more improvement when SI was decreasing during treatment (see Fig 2b, c). SI did not correlate with treatment response in inattention in either group.

Site differences

Sites significantly differed on multiple baseline variables, among which prescribed dosage; therefore, additional

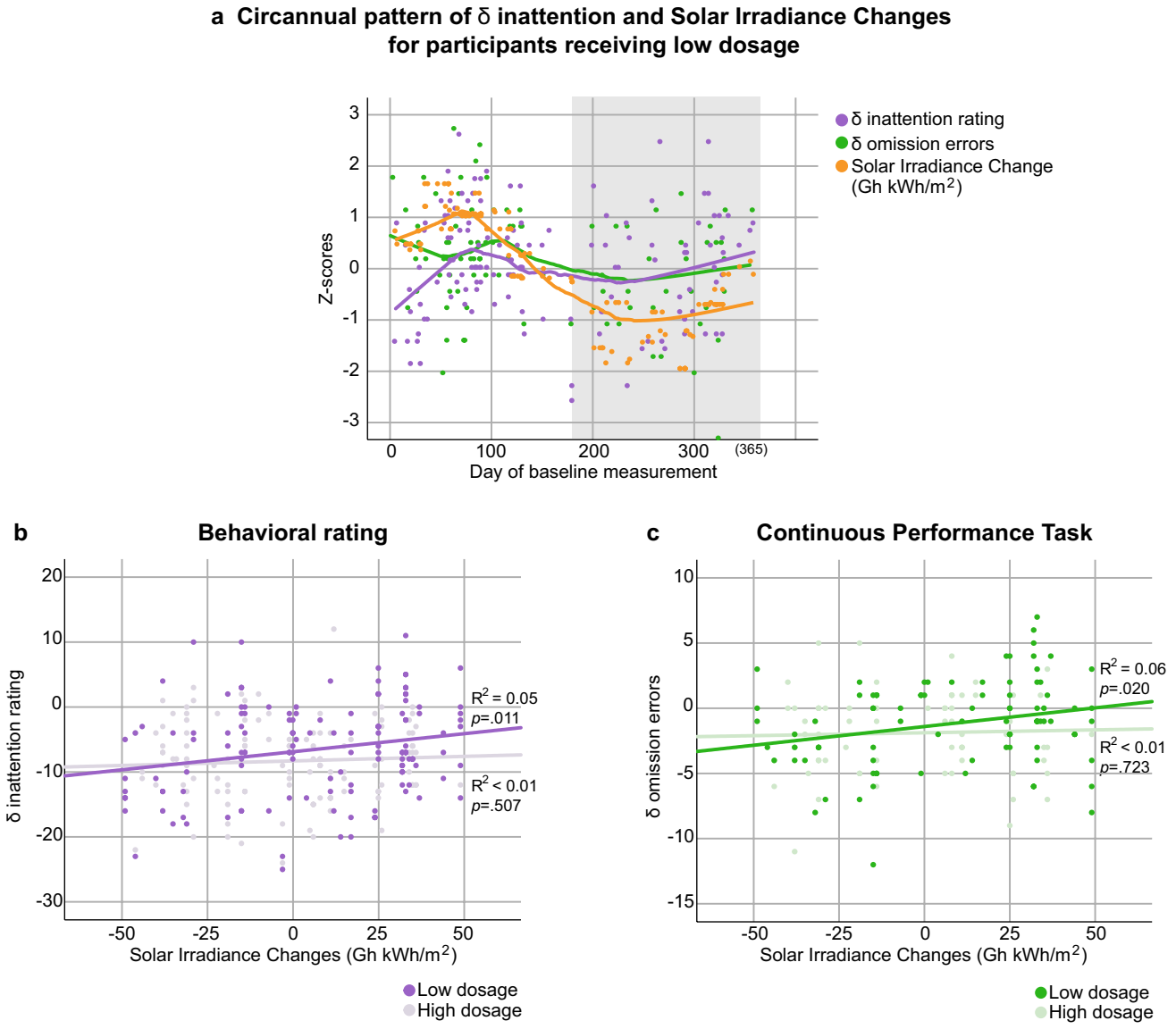

Fig. 2 The relationship between the treatment response and solar irradiance changes following baseline: **a** circannual variation (Loess fits) after *z*-transformation using the primary (inattention ratings) and secondary (omission errors on the continuous performance task) outcome measures for the low-dosage group, and correlations between solar irradiance change following baseline and **b** inattention ratings, and **c** omission errors on the continuous performance task for low and high dosages. *NB* a more negative value implies a better outcome

analyses were performed to confirm that site differences did not explain all observed effects.

These results confirm the observed circannual variation in treatment response, but, at the same time, suggest that it cannot be excluded that dosage dependence of treatment effects (during winter–summer) reflects other differences between sites (especially colton vs the other sites) (see supplement).

Discussion

We studied annual variation in inattention in ADHD patients receiving MPH treatment. We predicted least baseline inattention during a period of high sunlight intensity implying more room for improvement when sunlight intensity is low.

Inattention at treatment initiation did not annually vary, hence also lacked implied variation in room for improvement. We did, however, find an annual pattern in inattention at endpoint for low-dose treated patients. Patients treated with a high dose had significantly better attention than with a low dose, only when treated in winter–summer period. During summer–winter period, low-dosed treatment resulted in attention ratings similar to those treated with high dosage. These effects were also observed embracing the wide geographic nature of the current multicenter data set by studying the relationship between SI and inattention change. Although SI per se was not related to inattention before or after treatment, changes in SI were negatively related to attentional improvement specifically after low-dosed treatment. That is, a larger reduction in SI after treatment initiation coincided with a better treatment response. All the above described findings were primarily found in inattention ratings and replicated in omission errors on a CPT.

The lack of annual variation in inattention at baseline suggests that the previously reported relationship between prevalence rates of ADHD and geographical areas varying in sunlight intensity [1] is not gradual within the ADHD sample and is more likely explained by cumulative geographic effects—operating over a longer time-scale—rather than—more rapid—annual variation in sunlight intensity.

Daylight and inattention have been proposed to be related via mediation of the circadian system [5]. Studies directly investigating the circadian system demonstrated that prior light history (de)sensitizes the circadian clock to light, both in mice [controlled light–dark cycles [10]] and in humans [11]. Methylphenidate (MPH) also impacted the clock in mice (e.g., [12]), but has not been studied in humans yet. The antidepressant citalopram has been studied in humans and significantly increased the melatonin suppression response to light relative to placebo [13], demonstrating an interaction between pharmacological treatment and responsiveness to light in humans. The here reported largest MPH response with decreasing daylength (as in the summer–winter period) if low-dosed suggests that MPH treatment is most effective when light history is higher than current light exposure. MPH could, therefore, be hypothesized to work via impacting circadian clock sensitivity, thereby improving attentional functioning. In addition, we found a circannual pattern for low-dosed patients in particular. Receiving a high-dosage MPH may overshadow the effects of light changes, although site differences may have contributed to this finding, thus requiring follow-up. In line with the circadian pathway hypothesis [5], results were less pronounced for hyperactivity/impulsivity ratings and CPT commission errors.

The reported variation in MPH response implies that when starting treatment during the period of decreasing daylength (i.e., summer to winter), a low-dosage MPH suffices. Furthermore, results suggest that one mechanism of MPH may be to enhance sensitivity to the diurnal entrainment to sunlight. MPH affects the dopaminergic and noradrenergic systems. Particularly, the dopaminergic system is understood to be under profound circadian control [14]. Dopamine is produced in the amacrine cells of the retina [15]. As we can imply from its function to entrain to daylight by passing light information to the suprachiasmatic nucleus (SCN; our main biological clock), the retina is an important circadian organ. Circadian activity in the retina is dependent on both dopamine as well as the ‘night hormone’ melatonin [15]. Dopamine has an inhibitory effect on melatonin release and vice versa [16]. While dopamine is mainly synthesized and released in the early morning and during the day, melatonin is released in the evening and peaks at night [17]. Impaired retinal dopamine synthesis results in circadian rhythm fluctuations [18]. Based on an extensive review of the literature, we have hypothesized that impaired functioning of light sensitive retinal cells in ADHD subgroups may have its reflections on the melatonin and dopamine-producing cells in the retina, thereby having a role in the circadian misalignment as seen in the majority of ADHD patients [19]. Combining ‘light intake’ with MPH intake may be impacting the dopaminergic system through different routes, thereby possibly increasing the total impact. This possibility raises the question whether appropriate lighting could potentiate stimulants. Future studies could investigate if combining modulated light therapy with MPH intake (similar to the beneficial combination treatment of bright light and fluoxetine in nonseasonal depression [20]), increases its responsiveness, reaching optimal treatment outcome with minimal dosage throughout the year. A modulated version of light therapy, where particularly

changes in light exposure are created, would be crucial in establishing an environment that could likely potentiate stimulants.

Acknowledgements We acknowledge the iSPOT-A Investigators Group, the contributions of iSPOT-A principal investigators at each site, and the central management team (global coordinator Claire Day, PhD).

Compliance with ethical standards

Conflict of interest MA reports research grants and options from Brain Resource (Sydney, Australia) and shares from neuroCare Group (Munich, Germany); DP has received income and stock options with the role of science and data processing manager as an employee with Brain Resource Ltd.; EG is founder and receives income as Chief Executive Officer and Chairman for Brain Resource Ltd. He has stock options in Brain Resource Ltd. JKB has been a consultant to/member of advisory board of/and/or speaker for Janssen Cilag BV, Eli Lilly, and Servier in the past years. He is not an employee of any of these companies, and not a stock shareholder of any of these companies. He has no other financial or material support, including expert testimony, patents, royalties. MV, LK, TD, and GE report no financial disclosures.

Ethical approval The study complies with the principles of the "Declaration of Helsinki 2008," the International Conference on Harmonization (ICH) guidelines, and the laws and regulations of the country in which the research is conducted, including the principles of "Good Clinical Practice" as outlined in the U.S. Code of Federal Regulations. All sites received approval from their Institutional Review Board (IRB)/Independent Ethics Committee (IEC) prior to participant enrollment and each participant (and/or guardian) provided their informed consent to be involved in the study.

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