ORIGINAL ARTICLE

Frontal activation patterns during Tetris game play and estimated differences between high and low performers: a preliminary functional near-infrared spectroscopy study

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Abstract

Tetris has recently expanded its place of activity not only to an entertainment but also to clinical applications such as cognitive training and prevention of trauma flashback. However, to our knowledge, no studies focused on cortical activation patterns themselves when playing Tetris in a natural form. This study aimed to investigate activation patterns in the frontal cortex during naturally-performed Tetris in healthy subjects using functional near-infrared spectroscopy robust to artifacts by motion and electric devices. We also attempted to explore the frontal areas required to play Tetris successfully. We measured activations at 52 frontal areas for 90 seconds during Tetris play in 24 subjects, and the activations and correlations among those were compared between the high and low performers. The results demonstrated that significant activations had two factors, each showing a similar activation pattern. One of the factors was distributed over the lateral prefrontal cortex bilaterally, and the other was localized to the right prefrontal cortex. Moreover, exploratory analyses estimated that the activations of the areas centered on the right dorsolateral prefrontal cortex (DLPFC) increase and correlations of the activations between those areas and the other areas decrease, in the high performers compared with the low performers. In Conclusion, playing Tetris significantly activated both sides of the lateral prefrontal cortex. Furthermore, it was suggested that the high performers probably reduce functional connectivity between activations of the areas centered on the right DLPFC and the other areas, and increase the local activations compared with the low performers. This study would give important suggestions not only for information on brain activation patterns during Tetris play but also for the future development of neurocognitive clinical interventions using Tetris.

Key words: *Frontal cortex, Functional near-infrared spectroscopy, Oxygenated hemoglobin, Tetris, Visuospatial cognition*

INTRODUCTION

This preliminary study is the first step in the search for evidence-based tasks that can be used for neurocognitive clinical interventions with less burden, including rehabilitation, and can be performed even alone as sustainable homework. In this study, we adopted Tetris game, which demands relatively simple cognitive and motor functions to be performed, and explored the relationship between the execution of that game and frontal lobe activation in healthy subjects.

Tetris is the precursor of falling block puzzle computer games that has attracted many people worldwide over three decades. Studies using Tetris have been conducted across various disciplines mainly in the field of behavioral and cognitive sciences (Haier, 1992a, b, 2009; De Lisi, 2002; Holmes, 2009, 2010; Miller, 2011; Rietschel, 2012; Belchior, 2013; Nouchi, 2013; Price, 2013; Yoshida, 2014; Harmat, 2015; Lindstedt, 2015; Skorka-Brown, 2015; James, 2016; Sibert, 2017; Bikic, 2017; Iyadurai, 2018; Lau-Zhu, 2017; de Sampaio Barros, 2018; Meneghetti, 2018; Gold, 2019; Milani, 2019; Butler, 2020). As a neurocognitive clinical intervention, initially, Tetris was expected to be used for cognitive training due to the cognitive effects associated with the game (e.g. improvement of attention, mental rotation and visuospatial working memory) (De Lisi, 2002; Belchior, 2013; Nouchi, 2013; Bikic, 2017; Milani, 2019). Recent studies have also attempted to use Tetris for prevention of traumatic flashbacks (e.g. Holmes, 2009, 2010; James, 2016; Iyadurai, 2018; Butler, 2020), and most of those studies have been based on the assumption that the visuospatial cognitive loads of Tetris compete with the build-up of intrusive traumatic memories in the brain. Other studies have also demonstrated that playing Tetris may reduce drug cravings through competing visuospatial loads (Skorka-Brown, 2015). Important features of Tetris that make it suitable for clinical application include the fact that people of different cultures and with different cognitive levels are able to play Tetris with minimal instructions, having a high level of motivation and compliance because it is a worldwide recreational game which can be conducted on various computer platforms non-verbally (it was certified in Guinness World Records as "most ported videogame") (Guinness World Records, 2010; Ackerman, 2016).

There are few studies investigating brain activity related to Tetris play (Haier, 1992a, b, 2009; Rietschel, 2012; Price, 2013; Yoshida, 2014; Harmat, 2015; de Sampaio Barros, 2018). Moreover, to our knowledge, reference data of functional neuroimaging in healthy subjects during playing Tetris in a natural form has not been published yet. Such data is also important in advancing the evidence-based neurocognitive clinical application of Tetris. Therefore, this study aimed to detect cortical activation patterns during playing Tetris using functional near-infrared spectroscopy (fNIRS).

fNIRS is a non-invasive neuroimaging technique, which requires less restriction than other neuroimaging methods such as positron emission tomography (PET), functional magnetic resonance imaging (fMRI) and magnetoencephalography (MEG). It shows low sensitivity to artifact by motion and electric devices, and based on these properties, fNIRS has also been reported to be useful for evaluating the effects of rehabilitative interventions and neurofeedback training. (Mihara, 2016; Yang, 2019). In addition, considering its high portability and low cost, the use of fNIRS is expected to spread worldwide (for a review see Pinti, 2020). In fNIRS, near-infrared light penetrates into tissues and is differentially absorbed by hemoglobin depending upon the oxygenation state and its optical path length in the tissues (modified Beer–Lambert Law). This relationship enables fNIRS to detect relative changes in concentration of oxygenated hemoglobin ([oxy-Hb]) and deoxygenated hemoglobin ([deoxy-Hb]) by emitting near-infrared light at several different wavelengths into the cortex and detecting its remnants (Jöbsis, 1977; Hoshi, 2003; Ferrari, 2004). Areas with high neural activity show increased oxygen consumption followed by supply of oxygenated hemoglobin (neurovascular coupling) (Fox, 1986; Hoshi, 2001). This means that neural activity is measured indirectly by using relative changes in regional cerebral blood volumes (rCBV).

To our knowledge, there are three English articles using fNIRS during Tetris play (Yoshida, 2014; Harmat, 2015; de Sampaio Barros, 2018). However, these studies used Tetris to induce subjective flow experience without an interest of the underlying neural activation patterns of playing Tetris per se. Additionally, the cortical area analyzed in those studies was much smaller than that of our study. The results of these previous studies seem to indicate that the bilateral ventrolateral prefrontal cortex, the right dorsolateral prefrontal cortex (DLPFC) and the right inferior parietal lobe are significantly activated by Tetris play (de Sampaio Barros, 2018; Yoshida, 2014).

Using functional neuroimaging techniques, other than fNIRS, Tetris was first studied by Haier et al. (1992a), using PET in eight healthy male high performers trained intensively in Tetris. These subjects showed decreased metabolism over all brain areas induced by Tetris training. This led authors to conclude that activity of brain cortical areas was reduced by learning. They also reported that cortical metabolism after Tetris training could increase in the areas needed for high Tetris performance, including the right precuneus and left cingulate (Haier, 1992b). Using fMRI, Haier et al. (2009) demonstrated significant BOLD-signal increases in precentral gyrus, superior parietal lobule, inferior parietal lobule, and occipital gyrus (after a 3-month training) during playing Tetris in 15 healthy females. In addition, cortical thickness increased in left superior frontal gyrus and anterior superior temporal gyrus after training Tetris. Another fMRI study showed significant BOLD-signal increases in the right occipital cortex and the left DLPFC during Tetris play (Price, 2013). However, in these functional neuroimaging studies, Tetris was performed under restricted experimental conditions. Thus, it is difficult to consider that cortical activation patterns were investigated during naturally-performed Tetris. Only an electroencephalography (EEG) study investigated neural activation and network activity during naturally-performed Tetris. In the study, the activations were measured on Fz, F3, F4, C3, C4, T3, T4, P3, P4, O1, and O2 of the international 10/20 system for EEG, and the network activities were investigated between Fz and the other measurement points. Its findings showed increasing activations across the cortical areas and elevated network activities between the motor planning area in the frontal cortex (Fz) and the other cortical areas (the sensory and executive brain regions) as difficulty of Tetris increases (Rietschel, 2012).

Based on the findings of previous Tetris studies, we hypothesized that significant activation would be found in the lateral prefrontal cortex. Furthermore, as an exploratory investigation we attempted to seek frontal areas required to play Tetris successfully taking into account the relation between activation and performance.

MATERIALS AND METHODS

Subjects

Twenty-four right-handed healthy Japanese subjects participated in this study (13 men, 11 women; mean age ± standard deviation (SD) 27.3 ± 6.8 years). None of them had history of psychiatric or neurological disorders.

Written informed consent was obtained from all the subjects before the experiments. The procedures and methods in this study were consistent with the policies described in the Declaration of Helsinki. This research was approved by the Ethics Committee of Osaka University Graduate School of Medicine.

fNIRS measurement

Relative changes in [oxy-Hb] and [deoxy-Hb] were measured by using fNIRS (ETG-4000; Hitachi Medical Corporation, Tokyo, Japan) at temporal resolution of 100 msec during playing Tetris. In this study we used the ETG-4000's probe mounted with fifty-two measurement points (channels). Seventeen laser diodes (emitters) and sixteen photodiodes (detectors) were arranged reciprocally at 3 cm intervals on a piece of thermoplastic shell (3×11) covering most of the frontal and part of the temporal surface areas (Figure 1). Detection depth at the channels was 2–3 cm under the scalp. The lowest center photodiode was located on Fpz using the international 10/10 system for EEG. The channels set at the most

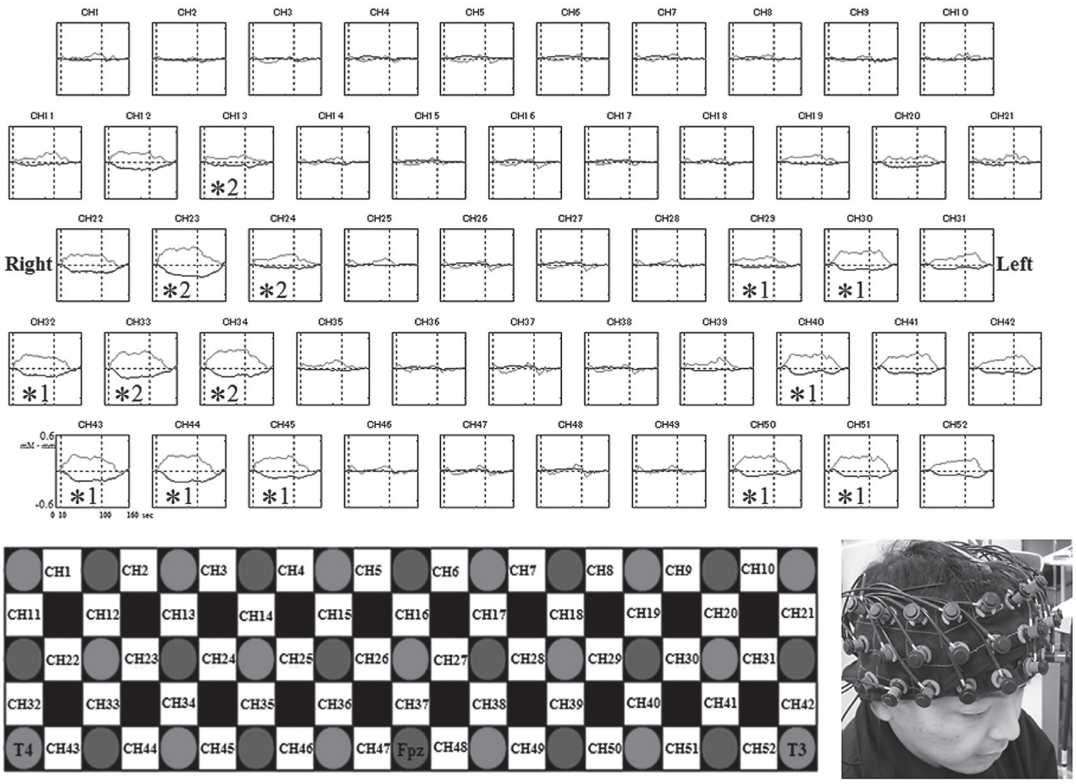

Figure 1. Grand average waveforms of changes in [oxy-Hb] (red) and [deoxy-Hb] (blue) during Tetris play for all channels, and arrangement of measurement points (channels) and optical diodes. In the upper diagram, the x-axis denotes time from 0 to 160 sec and the y-axis denotes activation between -0.6 and 0.6 mM·mm. The task period is shown by two vertical dashed lines at 10 and 100 sec. Picture on the bottom right shows the actual attached probe (written informed consent was obtained from the individual for the publication of this image). Schematic diagram on the bottom left presents the channels 1–52 as white squares among emitters (laser diodes, red circles) and detectors (photodiodes, blue circles) with the locations of Fpz, and T3, T4 (approximate) using the international 10/10 system for EEG. *1, *2, Fourteen significantly activated channels detected by single-sample *t*-tests with FDR correction and the number indicates the factor derived by a factor analysis using major factor method with direct oblimin rotation; CH, channel

lateral posterior edges corresponded to the T3-Cz-T4 row of the international 10/20 system or a little anterior to this row. The cortical region/channel association of this setting had been determined by the virtual registration method of fNIRS with automated Talairach atlas labels for functional brain mapping, which enables probabilistic registration for standalone fNIRS channel positions onto the Talairach stereotactic coordinates without the subject's MRI (Tsuzuki, 2007, 2014; Jichi Medical University, 2010). Accordingly, in order to interpret the cortical region/channel association in our study, we referred to it and a study on the anatomical correlation of EEG sensors, as well as studies using the virtual registration method of fNIRS (Koessler, 2009; Jichi Medical University, 2010; Yokoyama, 2015; Tomita, 2017).

Tasks

In the present study Tetris was adopted as the activation task. Tetris was performed using Nintendo Game boy pocket (Nintendo, Kyoto, Japan) which is a handheld game console. In this version of Tetris, on the monochrome liquid crystal display the player moves and rotates blocks that fall one by one. There are seven kinds of blocks consisting of four square blocks called Tetrimino. Tetrimino is moved by the cruciform button under the left thumb and rotated by the two round buttons under the right thumb aiming to arrange Tetrimino without gaps at the bottom. The lines vanish at the moment when they are made, and numbers of the deleted lines are recorded as LINE, which represents the behavioral data collected in this study. In addition, the upcoming Tetrimino is shown in the Preview box of the right side on the display.

In the baseline task, consisting of a resting state before and after Tetris execution, subjects were instructed to gaze at the display and tap their right and left thumbs reciprocally on the buttons of the console at a uniform pace.

Experimental procedure

Before the experiment, the subjects played Tetris for several minutes to confirm they knew how to play the game. Tetris used in this study can produce the game version from Level 0 to Level 9 in order from the one with the lowest falling speed of Tetrimino (blocks), and at first, we intended to have the subjects play Level 0 Tetris. However, if the subjects answered "Yes" to the question of whether you are good at Tetris and the fact was confirmed during the above pre-experimental play, we applied Level 1 Tetris to the subjects because we predicted that Level 0 would be too easy to induce the cortical activations particular to playing Tetris for them (Haier, 1992a; de Sampaio Barros, 2018). Accordingly, the subjects were given tasks closer to the individual optimal levels of difficulty, which had been shown to induce more right prefrontal activation than the easy or hard level during Tetris play (de Sampaio Barros, 2018). In this study, 9 subjects played Tetris at Level 1 and 15 subjects played at Level 0, and as expected, LINE (the number of lines deleted by the player) of those who played at Level 1 was up to the top ninth LINE.

During the experiment, the subjects sat on a chair in a silent room. The subjects executed the baseline task (30 sec), Tetris game (90 sec), and the baseline task (60 sec). Instructions were given orally. We previously succeeded in determining activation patterns during cognitive and motor tasks by using the same procedure with the ETG-4000 (Nakahachi, 2008, 2010, 2015, 2016).

Data analysis

・*Preparation*

Relative changes in [oxy-Hb] and [deoxy-Hb] are defined as the product of the concentration of hemoglobin and optical path length, and are expressed in the unit of mM·mm. Changes in [oxy-Hb] at every 100 msec were analyzed, which are considered to be most sensitive to changes in rCBV and strongly correlate with the BOLD signal of fMRI, while the direction of [deoxy-Hb] changes is influenced by changes in blood oxygenation and volume of the vein (Hoshi, 2001, 2003; Scarapicchia, 2017).

The analysis software of ETG-4000 was set at the "integral mode". In that configuration, mean changes in [oxy-Hb] for the baseline states 10 sec before the start of the activation task and after 50 sec from the finish of the activation task, were corrected to 0 mM·mm by using linear fitting. The activation task period was set at 90 sec, and the recovery period from the finish of the activation task period up to baseline stabilization was set at 50 sec. The moving average method for 5 sec was applied to smooth out short-term motion artifacts.

・*Detection of activation patterns*

In statistical analyses, firstly, the authors determined frontal activation patterns during Tetris play. Mean changes in [oxy-Hb] during Tetris play were calculated for each subject in each channel, followed by a two-tailed single-sample *t*-test, which is equal to a paired Student's *t*-test against zero (mean changes in [oxy-Hb] during baseline periods) to detect significant activation. Because the two-tailed single-sample *t*-tests were conducted on all fifty-two channels, the significant α levels of 0.05 were corrected by the false discovery rate (FDR) to control multiple comparisons (Benjamini, 1995), which had been applied to fNIRS study (Singh, 2006). Next, we expected that components of the Tetris-induced activations would be classified by the functions, and this may give suggestion of the cortical areas to successfully perform Tetris, so that the following analysis was carried out. In order to extract channel groups showing similar patterns of changes in [oxy-Hb] from the significantly activated channels by the above single-sample *t*-test, factor analysis using major factor method with direct oblimin rotation was performed on mean changes in [oxy-Hb] during Tetris play of the subjects in those channels. The number of factors was determined according to the Kaiser-Guttman rule. In each channel, the extracted factor, which indicated the absolute value of factor loading after direct oblimin rotation over 0.4 and higher than the other factors, was selected as the represented factor of the channel. Also, mean changes in [oxy-Hb] of each subject during Tetris play were averaged among the channels belonging to each extracted factor, and compared using paired Student's *t*-test. All statistical tests were conducted using SPSS software version 21 (IBM Japan).

- ***Exploratory analyses seeking activations for high performance***

Pearson's correlation coefficients between LINE and the mean values of [oxy-Hb] changes during Tetris play in the subjects were calculated for each channel. Next, the twenty-four subjects were divided into three equal parts of high, middle and low performer groups each with 8 members, in order of LINE values. One-way ANOVA using Tukey correction for multiple comparisons was performed on the mean changes in [oxy-Hb] between the three groups in each channel. Moreover, to investigate differences in LINE in detail, independent Student's *t*-test was carried out to compare the mean changes in [oxy-Hb] between the high and the low performer groups (8 members respectively) in each channel. Furthermore, based on the findings of Rietschel et al. (2012), that the cortical network activity, i.e. functional connectivity measured by EEG increases as the difficulty of Tetris increases, we predicted that functional connectivity would be reduced in the high performer group compared with the low performer group, particularly in cortical areas required for playing Tetris successfully. Thus, the following analyses were carried out. In each channel, Pearson's correlation coefficients were calculated for the mean changes in [oxy-Hb] between the one channel and the other 51 channels, and the 51 Pearson's correlation coefficients were averaged. Paired Student's *t*-test was performed on the 52 averaged values of the Pearson's correlation coefficients between the low and high performer groups. Also, in each channel, the 51 Pearson's correlation coefficients were compared by paired Student's *t*-test between the two groups. In the above analyses, when controlling multiple comparisons, the significant α levels of 0.05 were corrected by FDR. And, we subsequently searched for the channels with the statistic values greater than the mean + 2 SD in order to estimate the frontal areas for successfully performing Tetris.

RESULTS

Activation patterns

The grand average waveforms of changes in [oxy-Hb] across all the subjects were obtained for each channel by using MATLAB R2014a (MathWorks) (Figure 1). Fourteen channels (26.9%) demonstrated significant increases in [oxy-Hb] on a single-sample *t*-test with FDR correction (*d.f.* = 23, *t* = 2.727 to 4.137, *p* = 0.0120 to 0.0004) (Figure 1), and the highest *t* value was shown in channel 24 (*t* = 4.137) (Table 1). Factor analysis using major factor method with direct oblimin rotation was performed on mean changes in [oxy-Hb] during Tetris play of these significantly activated 14 channels. The Kaiser-Meyer-Olkin measure of sampling adequacy (*p* = 0.813) and Bartlett's test of sphericity (*d.f.* = 91, χ^2 = 446.36, *p* = 2.723E-48) guaranteed the validity of applying factor analysis. Two factors accounting for 79.289% of the total variance were extracted. While the channels with large factor loading of factor 1 were distributed on both sides of the prefrontal cortex, the channels with large factor loading of factor 2 were confined to the right side of the prefrontal cortex (Figure 1). Additionally, there were no significant differences (*d.f.* = 23, *t* = 0.003, *p* = 0.998) among averages of mean changes in [oxy-Hb] during Tetris play in those channels belonging to each of the factor 1 and factor 2 (the average ± SD: 0.181 ± 0.229, 0.181 ± 0.247, respectively).

Table 1. Individual channel values related to frontal cortical activation

Right channel	Activation	*t* (*p* value)
CH1	0.029±0.154	0.93(0.362)
CH2	-0.006±0.148	-0.208(0.837)
CH3	-0.025±0.147	-0.847(0.405)
CH4	-0.005±0.099	-0.262(0.796)
CH5	-0.013±0.116	-0.554(0.585)
CH11	0.079±0.19	2.028(0.054)
CH12	0.14±0.26	2.632(0.015)
CH13	0.075±0.128	2.874(0.009)*
CH14	0.019±0.112	0.836(0.412)
CH15	-0.002±0.075	-0.152(0.88)
CH22	0.145±0.281	2.528(0.019)
CH23	0.239±0.393	2.986(0.007)*
CH24	0.116±0.137	4.137(0.0004)*
CH25	0.044±0.099	2.193(0.039)
CH26	-0.006±0.107	-0.261(0.796)
CH32	0.178±0.221	3.935(0.001)*
CH33	0.223±0.298	3.667(0.001)*
CH34	0.251±0.357	3.437(0.002)*
CH35	0.068±0.161	2.071(0.05)
CH36	0.002±0.168	0.053(0.958)
CH43	0.204±0.264	3.787(0.001)*
CH44	0.214±0.299	3.507(0.002)*
CH45	0.193±0.271	3.485(0.002)*
CH46	0.023±0.227	0.488(0.63)
CH47	0.003±0.172	0.085(0.933)

Left channel	Activation	*t* (*p* value)
CH6	0.004±0.123	0.166(0.869)
CH7	0.015±0.103	0.733(0.471)
CH8	0.015±0.14	0.509(0.615)
CH9	-0.004±0.132	-0.138(0.892)
CH10	0.003±0.113	0.11(0.913)
CH17	-0.004±0.107	-0.162(0.873)
CH18	0.021±0.123	0.833(0.413)
CH19	0.082±0.161	2.487(0.021)
CH20	0.05±0.212	1.165(0.256)
CH21	0.051±0.179	1.399(0.175)
CH27	-0.005±0.151	-0.16(0.874)
CH28	0.027±0.135	0.98(0.337)
CH29	0.095±0.172	2.727(0.012)*
CH30	0.173±0.24	3.541(0.002)*
CH31	0.087±0.238	1.798(0.085)
CH38	-0.008±0.186	-0.219(0.828)
CH39	0.084±0.198	2.082(0.049)
CH40	0.186±0.279	3.26(0.003)*
CH41	0.163±0.308	2.589(0.016)
CH42	0.111±0.23	2.367(0.027)
CH48	0.019±0.199	0.472(0.641)
CH49	0.015±0.195	0.383(0.706)
CH50	0.198±0.275	3.53(0.002)*
CH51	0.187±0.319	2.87(0.009)*
CH52	0.114±0.323	1.726(0.098)

Middle channel	Activation	*t* (*p* value)
CH16	-0.009±0.115	-0.362(0.72)
CH37	-0.006±0.163	-0.178(0.86)

Activation, the average across 24 participants' mean values of changes in [oxy-Hb] ± SD (mM·mm) during Tetris play in each channel; *t*, the *t* values derived by comparing the 24 participants' mean changes in [oxy-Hb] during Tetris play with the baseline using a single-sample *t*- test; *, significance after FDR correction; CH, channel

Differences in activations between high and low performers

・*Correlation between activations and LINE*

Pearson's correlation analysis between LINE and mean changes in [oxy-Hb] during Tetris play was carried out in each channel, and significant channels were not found after FDR correction.

・*Comparison of activations between groups based on the difference in LINE*

Based on LINE values (the mean ± SD: 8 ± 4), 24 subjects were divided into three groups of 8 subjects each, named high (13 ± 1), middle (7 ± 2), and low (3 ± 2) performers. One-way ANOVA in each channel found no significant channel after FDR correction. Independent Student's *t*-test of mean changes in [oxy-Hb] during Tetris play in each channel between the high and low performers also showed no significant channel after FDR correction.

・*Comparison between high and low performers on correlation coefficients of activations among channels*

The average ± SD of 52 mean values of 51 Pearson's correlation coefficients between each channel and the other 51 channels were 0.385 ± 0.161 for the high performers and 0.554 ± 0.108 for the low performers. Comparing with a paired Student's *t*-test, it was found that the correlation between channels significantly increased in the low performers compared with the high performers (*d.f.* = 51, *t* = 5.722, *p* = 5.570E-07). In each channel, Paired Student's *t*-test between the two groups for the 51 Pearson's correlation coefficients showed significant differences in twenty-nine channels after FDR correction (*d.f.* = 50, *t* = 2.378 to 13.602, *p* = 0.021 to 1.981E-18) (Figure 2).

・*Estimation of differences in activations between high and low performers*

For the same items as mentioned above, the frontal areas for successfully performing Tetris were estimated using the channels indicating the statistical values greater than the mean + 2 SD. Pearson's correlation analyses between LINE and activations during Tetris play did not show such a channel. For reference, the channel with the highest correlation coefficient was channel 24 (*r* = 0.294, *p* = 0.163), and the channels belonging to factor 2 in the above factor analysis showed $r > 0.20$ while those belonging to factor 1 showed $|r| < 0.135$ (Table 2, Figure S1). One-way ANOVA between the three groups found that channel 24 was the only channel with the statistic value greater than the mean + 2 SD ($F > 2.221$) (Figure 3, Table 2). Multiple comparisons conducted in channel 24 by Tukey's method revealed that the activation of the high performers significantly increased compared with that of the low performers (*p* = 0.0499). The statistic values calculated by independent Student's *t*-test between the high and low performers were greater than the mean + 2 SD, in channels 12, 23,

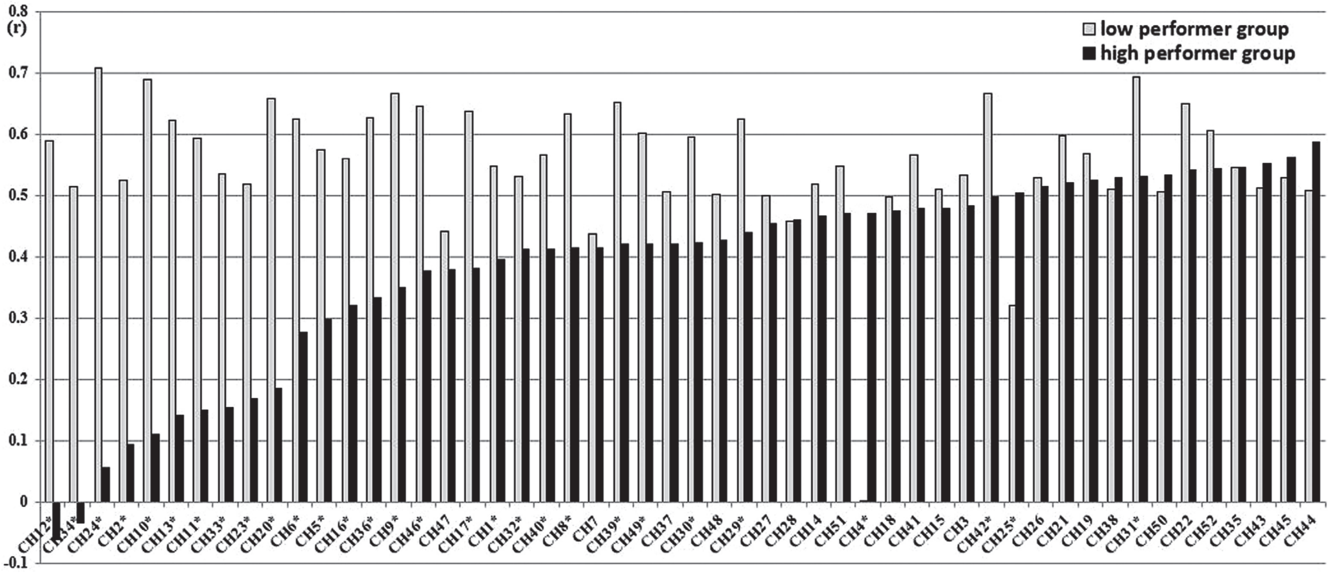

Figure 2. Averages of Pearson's correlation coefficients (*r*) between each channel and the other 51 channels for mean changes in [oxy-Hb] during Tetris play of each subject in the high and low performer groups. Bar graphs are arranged in ascending order for *r* of the high performer group. *, Twenty-nine significant channels after paired Student's *t*-test with FDR correction on the Pearson's correlation coefficients of mean changes in [oxy-Hb] among each channel and the other 51 channels between the two groups; CH, channel

Table 2. Individual channel values related to differences in frontal cortical activation by skill of Tetris play

Right Channel	*R*(*p* value)	*F*(*p* value)	*T*(*p* value)	*paired T*(*p* value)	Left Channel	*R*(*p* value)	*F*(*p* value)	*T*(*p* value)	*paired T*(*p* value)
CH1	-0.072(0.738)	0.782(0.47)	-0.083(0.935)	2.378(0.021)	CH6	0.242(0.255)	1.183(0.326)	1.254(0.23)	5.325(<0.001)
CH2	-0.164(0.445)	0.664(0.525)	-0.681(0.507)	6.6(<0.001)	CH7	0.223(0.295)	0.807(0.46)	1.178(0.258)	0.365(0.717)
CH3	-0.036(0.866)	0.066(0.937)	-0.284(0.781)	0.972(0.336)	CH8	0.036(0.868)	0.066(0.936)	0.292(0.775)	3.911(<0.001)
CH4	0.156(0.467)	0.041(0.96)	0.251(0.805)	-9.153(<0.001)	CH9	0.069(0.747)	0.299(0.744)	0.505(0.622)	8.209(<0.001)
CH5	0.105(0.625)	0.17(0.845)	0.501(0.624)	4.215(<0.001)	CH10	-0.084(0.697)	0.024(0.976)	0.016(0.988)	9.648(<0.001)
CH11	-0.226(0.288)	0.259(0.774)	-0.465(0.649)	9.049(<0.001)	CH17	0.196(0.359)	1.065(0.363)	1.24(0.235)	3.961(<0.001)
CH12	0.236(0.267)	2.105(0.147)	2.411(0.03)*	13.602(<0.001)*	CH18	0.05(0.816)	0.349(0.709)	0.754(0.463)	0.457(0.65)
CH13	0.208(0.328)	1.619(0.222)	1.613(0.129)	10.697(<0.001)	CH19	-0.026(0.902)	0.04(0.961)	0.128(0.9)	1.078(0.286)
CH14	-0.094(0.663)	0.125(0.883)	-0.472(0.644)	1.012(0.316)	CH20	0.074(0.733)	0.258(0.775)	0.637(0.534)	9.73(<0.001)
CH15	0.042(0.845)	1.368(0.276)	-0.019(0.985)	0.526(0.601)	CH21	0.146(0.495)	0.397(0.677)	0.755(0.463)	1.583(0.12)
CH22	-0.014(0.948)	0.82(0.454)	0.705(0.492)	1.743(0.087)	CH27	0.178(0.405)	1.354(0.28)	1.116(0.283)	0.757(0.453)
CH23	0.249(0.24)	2.04(0.155)	2.391(0.031)*	7.533(<0.001)	CH28	0.127(0.554)	0.559(0.58)	1.128(0.278)	-0.039(0.969)
CH24	0.294(0.163)	3.849(0.038)*	2.455(0.028)*	13.57(<0.001)*	CH29	-0.118(0.583)	0.004(0.996)	-0.096(0.925)	3.693(0.001)
CH25	-0.178(0.406)	0.591(0.563)	-0.791(0.442)	-3.481(0.001)	CH30	0.131(0.541)	0.541(0.59)	0.865(0.401)	6.035(<0.001)
CH26	-0.074(0.73)	1.249(0.307)	0.023(0.982)	0.313(0.755)	CH31	0.209(0.328)	0.969(0.396)	1.075(0.301)	3.411(0.001)
CH32	0.105(0.625)	1.215(0.317)	1.212(0.246)	2.665(0.01)	CH38	0.107(0.619)	0.667(0.524)	1.236(0.237)	-0.349(0.728)
CH33	0.229(0.281)	2.099(0.148)	2.466(0.027)*	10.093(<0.001)	CH39	-0.104(0.63)	0.031(0.97)	0.155(0.879)	4.247(<0.001)
CH34	0.243(0.252)	1.978(0.163)	-1.935(0.073)	10.669(<0.001)	CH40	-0.063(0.769)	0.348(0.71)	0.362(0.723)	3.948(<0.001)
CH35	-0.025(0.906)	0.795(0.465)	0.122(0.905)	0.02(0.984)	CH41	0.24(0.259)	1.41(0.266)	1.565(0.14)	1.913(0.061)
CH36	-0.118(0.583)	0.212(0.811)	-0.213(0.835)	6.668(<0.001)	CH42	0.105(0.624)	0.752(0.484)	0.794(0.44)	3.123(0.003)
CH43	0.108(0.617)	1.275(0.3)	1.551(0.143)	-0.736(0.465)	CH48	0.111(0.607)	1.144(0.337)	1.53(0.148)	1.317(0.194)
CH44	0.019(0.928)	0.327(0.725)	0.85(0.41)	-1.064(0.292)	CH49	-0.149(0.488)	0.09(0.914)	0.198(0.846)	4.028(<0.001)
CH45	0.128(0.55)	0.635(0.54)	1.222(0.242)	-0.666(0.509)	CH50	-0.073(0.736)	0.15(0.862)	0.315(0.757)	-0.508(0.614)
CH46	-0.076(0.724)	0.094(0.911)	-.181(0.859)	4.598(<0.001)	CH51	-0.036(0.866)	0.228(0.798)	0.527(0.606)	1.359(0.18)
CH47	0.003(0.991)	0.51(0.608)	0.683(0.506)	1.138(0.26)	CH52	0.023(0.914)	0.231(0.795)	0.525(0.608)	1.054(0.297)

Middle Channel	*R*(*p* value)	*F*(*p* value)	*T*(*p* value)	*paired T*(*p* value)
CH16	0.13(0.545)	0.794(0.465)	0.867(0.401)	3.864(<0.001)
CH37	0.031(0.887)	0.45(0.644)	0.919(0.373)	1.614(0.113)

R, Pearson's correlation coefficients between the mean changes in [oxy-Hb] and LINE values during Tetris play in 24 subjects; *F*, the *F* values derived by one-way ANOVA for mean changes in [oxy-Hb] during Tetris play in subjects trisected into high, middle and low performer groups based on LINE values; *T*, the *t* values derived by comparing mean changes in [oxy-Hb] during Tetris play of the high performer group with that of the low performer group using independent Student's *t*-tests; paired *T*, the *t* values derived by comparing Pearson's correlation coefficients between each channel and the other channels for mean changes in [oxy-Hb] during Tetris play in the low performer group with those of the high performer group by using paired Student's *t*-test; *, the value > the mean + 2 SD; CH, Channel

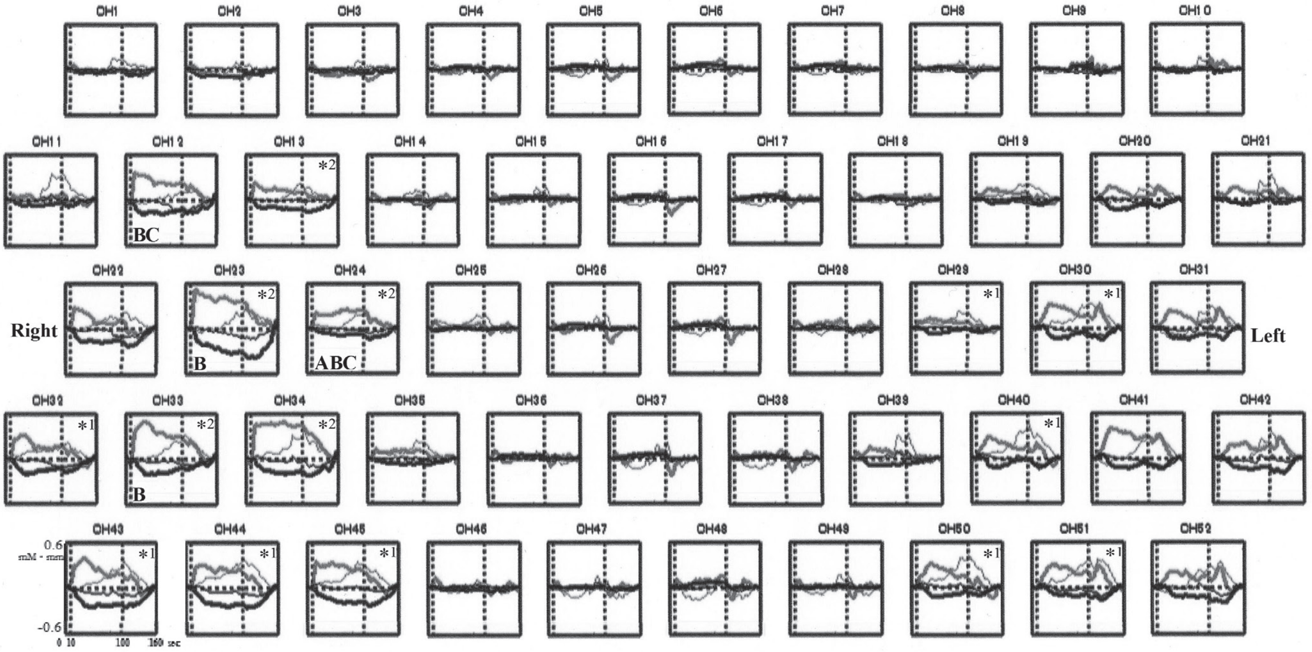

Figure 3. The high (thick line) and low (thin line) performer groups' grand average waveforms of changes in [oxy-Hb] (red) and [deoxy-Hb] (blue) during Tetris play for all channels. In each channel, the x-axis denotes time from 0 to 160 sec and the y-axis denotes activation between -0.6 and 0.6 mM·mm. The task period is shown by two vertical dashed lines at 10 and 100 sec. A, one channel that shows the F value > the mean + 2 SD derived by one-way ANOVA on the high, low, and middle performer groups' mean changes in [oxy-Hb] during Tetris play; B, four channels that show the *t* values > the mean + 2 SD derived by independent Student's *t*-tests on the high and low performer groups' mean changes in [oxy-Hb] during Tetris play; C, two channels that show the paired Student's *t* values > the mean + 2 SD when the Pearson's correlation coefficients between each channel and the other 51 channels for mean changes in [oxy-Hb] during Tetris play of each subject in the low performer group are compared with those in the high performer group. *1, *2, the same as in Figure1; CH, channel

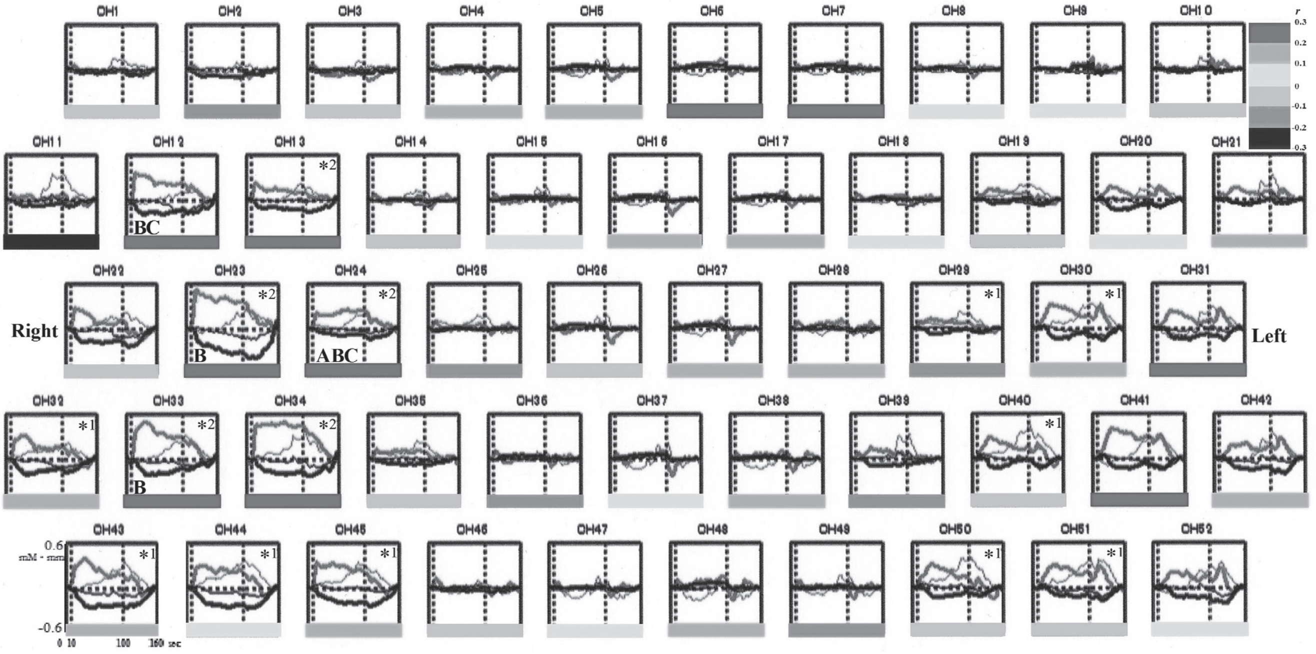

Figure S1. Additional information for Figure 3. Pearson's correlation coefficient (*r*) between the 24 participants' mean changes in [oxy-Hb] and LINE values during Tetris play is color coded in each channel.

24, and 33 ($t > 2.313$) (Figure 3, Table 2). The statistic values calculated by paired Student's *t*-test between the high and low performers in each channel on the correlation coefficients of activations among channels were greater than the mean + 2 SD, in channels 12 and 24 ($t > 12.023$) (Figure 3, Table 2).

DISCUSSION

Summary of results

In this study, we used fNIRS to determine frontal activation patterns in healthy subjects while playing Tetris. We found bilateral significant activations in 14 (26.9%) of the 52 channels investigated in both hemispheres (Figure 1, Table 1). Consistent with our hypothesis and with findings from previous fNIRS studies during Tetris play, significant activations in this study were detected in the lateral prefrontal cortex (Yoshida, 2014; de Sampaio Barros, 2018). Furthermore, factor analysis to extract channel groups showing similar activation patterns allowed us to extract two factors from these significantly activated 14 channels. Those channels with a large factor loading for the factor 2 were confined to the right-sided lateral prefrontal cortex Figure 1). Subsequently, exploratory analyses estimated that the channels on the frontal cortical areas necessary for successfully performing Tetris overlapped with those showing a large factor loading of factor 2 derived from the aforementioned factor analysis.

Estimating the frontal area for playing Tetris successfully

Among the channels estimated by using statistics above the mean + 2SD, channel 24 was the only channel estimated by the most exploratory analyses, and the other estimated channels appeared to be radially distributed rearward around channel 24 (Figure 3, Table 2). The cortical region/channel association of the channel 24 showed 100% agreement with Brodmann area (BA) 46 in the right dorsolateral prefrontal cortex by the virtual registration methods of fNIRS with automated Talairach atlas labels (the channels showing 100% agreement are rare except for BA 10) (Jichi Medical University, 2010). By using fNIRS, de Sampaio Barros et al. (2018) reported that in subjects showing great flow-state during Tetris play, activation of the right DLPFC and the right inferior parietal lobe were high although the measurement focused on only the two areas involved in the frontoparietal attentional network. This supports our finding that the high performers, many of who should achieve flow-state during Tetris play, were estimated to highly activate the right DLPFC while playing the game. Based on these arguments, we estimated that at least the right DLPFC (BA 46) would be a crucial frontal cortex area for successfully performing Tetris.

In previous studies, attention, mental rotation, working memory, planning and decision making during speeded manipulations for visuospatial tasks were mentioned as the main cognitive functions required for smooth performance of Tetris game (De Lisi, 2002; Haier, 2009; Holmes, 2009; Miller, 2011; Belchior, 2013; Nouchi, 2013; Harmat, 2015; Lindstedt, 2015; Skorka-Brown, 2015; Sibert, 2017; Bikic, 2017; Lau-Zhu, 2017; de Sampaio Barros, 2018; Meneghetti, 2018; Gold, 2019; Milani, 2019). There are studies suggesting that goal-directed smooth manipulations or executive control of these cognitive functions on visuospatial activity are closely related to the activation of the area centered on the right DLPFC (Smith, 1999; Semrud-Clikeman, 2012; Srovnalova, 2012; Funahashi, 2013; Giglia, 2014; Heinze, 2014; Wu, 2014; Colombo, 2016; Tomasino, 2016; Carter, 2017; Suzuki, 2018). Therefore, these studies support the fact that the right DLPFC is presumed to be most important in the frontal cortex for successfully performing Tetris in our study.

Functional connectivity

In this study, it is noteworthy that functional connectivity was quantitatively compared between the high and low performers to estimate the frontal cortex areas necessary for successfully performing Tetris by using a method based on the EEG evidence that cortical network activity increases as the difficulty level of Tetris increases (Rietschel, 2012). An interesting finding obtained was that functional connectivity declines in the high performers, mainly in the channels involved in the successful performance of Tetris. This phenomenon is likely related to the neural efficiency hypothesis, indicating that high performers exclude inefficient cortical functional connectivity, using the brain more efficiently than low performers (Haier, 1992a; Rypma, 2006; Neubauer, 2009; Lipp, 2012; Rietschel, 2012).

Clinical implication

The fact that frontal activations and connectivity during naturally performing Tetris were detected using fNIRS may support the availability of this method to quantitatively assess the neural effects of cognitive training with Tetris. Moreover, the estimated differences in the activations between the high and low performers imply that the cortical activation patterns can be changed by training using Tetris. Recently, it was reported that playing Tetris increases hippocampal volume (Butler, 2020). Regarding such morphological changes of the brain due to Tetris play, it has been reported that cortical thickness increase in the left superior frontal gyrus and anterior superior temporal gyrus (Haier, 2009). Thus, Tetris game play may be said to be noninvasive neuromodulative task based on evidence (See Budde, 2020 for the terminology usage).

As mentioned in the Introduction, so far neurocognitive clinical applications of Tetris for preventive interventions against traumatic flashbacks and drug cravings have been carried out based exclusively on the psychological assumption that playing Tetris should strongly stimulate the processing pathway of visuospatial cognitive loads (Holmes, 2009, 2010; Skorka-Brown, 2015; James, 2016; Iyadurai, 2018). In the present study, it was suggested that the aforementioned psychological assumptions were actually likely to be correct by the method of functional neuroimaging. Especially in the high performers, our findings may represent neurobiological evidence to boost the use of Tetris for such neurocognitive clinical interventions.

Limitations

This study has several limitations. First, using 24 subjects, we analyzed the activation pattern of the frontal cortex during the Tetris play and obtained significant results. However, in exploratory analyses to investigate the frontal cortical areas for successfully playing Tetris, statistical power was not enough because the subjects were divided into three equal parts based on their behavioral data. Thus, the small number of subjects may be the cause of extinguishing statistical significances after FDR correction. In the exploratory analyses, we reported the preliminary results in order to make hypotheses that should be proved in future studies using larger sample size. Second, [oxy-Hb] changes are expressed as relative values compared with baseline state, and it is assumed that optical path length would be constant across subjects and measurement points. Therefore, evaluations using this type of fNIRS (continuous wave-based) device that cannot measure the absolute values should be regarded as estimates (Pinti, 2020). Third, in the present study, we investigated only the frontal lobe. The previous studies using Tetris have also suggested the involvement of the parietal and occipital lobes (Haier, 1992a, b, 2009; de Sampaio Barros, 2018; Gold, 2019). In studies that compare high and low performers of cognitive tasks, such as this study, differences in strategy might show differences in activations at the brain lobe level. Therefore, it would be worth investigating across wide brain areas. Fourth, recent evidence indicates that signals of fNIRS may involve components from blood flow of the scalp (Takahashi, 2011; Kirilina, 2012). However, because strong correlations between fNIRS and fMRI signals have been reported (for a review see Scarapicchia, 2017), the activation seen in this study is thought to reflect considerable signals from neurons. Future development of techniques on fNIRS that can separate systemic signals from brain activity components is awaited.

Conclusions

The activations of the frontal cortex during naturally-performed Tetris were distributed over the lateral prefrontal cortex in both hemispheres, which was consistent with our hypothesis. The activations had two factors, one of which included the activations seemed to be associated with the Tetris performance confined in the right hemisphere and the other would be performance-independent activations in both hemispheres. Furthermore, our findings suggest that in order to elevate activations of the areas centered on the right DLPFC (BA 46) high Tetris performers probably disengaged them from unnecessary functional connections with other cortical areas to use the brain more efficiently, compared with low performers. Additionally, thus because the cortical activation patterns during Tetris play seem to be considerably different depending on the subject's performance, in order to effectively utilize Tetris play for neurocognitive clinical interventions, it would be necessary to consider whether its visuospatial cognitive loads stimulate the appropriate areas of the subject's brain (e.g. competing with visuospatial trauma memory). This might help explore better interventions and avoid wasting time applying ineffective interventions. Future studies will confirm and extend the findings of this study by using larger samples and/or by exploring brain activity during Tetris play in wider brain areas, ultimately with the aim of developing evidence-based novel neurocognitive clinical interventions.

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