KARYA TULIS ILMIAH

GAMBARAN KADAR HEMOGLOBIN PADA REMAJA *GAMER* PRIA

LITERATUR REVIEW

NURUL IKA INSHANI
17.131.0069

PROGRAM STUDI DIPLOMA III ANALIS KESEHATAN
SEKOLAH TINGGI ILMU KESEHATAN
INSAN CENDEKIA MEDIKA
JOMBANG
2020

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LITERATUR REVIEW

Tugas Akhir Literature Review

Diajukan Dalam Rangka Memenuhi Persyaratan

Menyelesaikan Studi di Program Diploma III

Analis Kesehatan

NURUL IKA INSHANI

171310069

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ABSTRACT

The Description of Hemoglobin Levels in Men's Gamers

Literature Review

By :

Nurul Ika Inshani

Gamers have the meaning "Someone who likes playing computer games". If it translates to "seseorang yang suka bermain game komputer", *then someone can be called a gamer if he likes playing games, no matter how big his skills, game collection, or insight into games. These gamers can lower hemoglobin or oxyHb. This decrease in oxyHb in DPFC is due to video games consisting of many stimuli such as color images and sound continuously, it is not clear which constituents of video games cause these hemodynamics to undergo changes in the experiment. This method uses literature reviews with key terms and phrases related to hemoglobin and gaming or gaming. Comprehensive database searches were carried out in scient direct (2006), ResearchGate (2014-2019), and Semantic scholar (2015) to obtain relevant journals. The results of the research from the five journals or articles reviewed found that most of the hemoglobin decreased.*

Key words: Hemoglobin, game

ABSTRAK
GAMBARAN KADAR HEMOGLOBIN PADA REMAJA *GAMER* PRIA

Literature Review

Oleh :
Nurul Ika Inshani

*Gamer*memilikiarti*"Someone who likes playing computer games"*. Jikaditerjemahkanmenjadi*"seseorang yang senangbermain game komputer (elektronik)"*, *m*aka seseorangbisadisebutsebagai*gamer*jikadiasukabermain*game*, takpeduliseberapabesarkemampuan, koleksi game, atauwawasannyatentang game. Pada gamer ini dapat menurunkan hemoglobin atau oxyHb. Penurunan OxyHb di bagian DPFC ini dikarenakan video game terdiri dari banyak rangsangan seperti gambar berwarna dan suara terus menerus, tidak jelas yang konstituen dari video game menyebabkan hemodinamik tersebut mengalani perubahan dalam percobaan. Metode ini menggunakan literatur review dengan istilah dan frasa kunci yang terkait dengan hemoglobin dan gaming atau game. Pencarian database yang komprehensif dilakukan di Scient direct (2006), ResearchGate (2014-2019), dan Semantic scholar (2015) untuk memperoleh jurnal yang relevan. Hasil penelitian dari kelima jurnal atau artikel yang direview didapatkan sebagian besar hemoglobin menurun.

Kata kunci : Hemoglobin, Game

LEMBAR PERSETUJUAN KARYA TULIS ILMIAH

Judul	: Gambaran Kadar Hemoglobin pada Remaja *Gamer* Pria
Nama Mahasiswa	: Nurul Ika Inshani
Nomor Pokok	: 171310069
Program Studi	: Diploma III Analis Kesehatan

Menyetujui,

Komisi Pembimbing

Lilis Majidah, S.Pd., M.Kes
NIK. 01.12.547

Ummaysaroh, S.ST
NIP. 19711206199732006

Mengetahui,

Ketua STIKes ICMe

H. Imam Fatoni, S.KM., MM
NIK. 03.04.022

Ketua Program Studi

Sri Sayekti, S.Si., M.Ked
NIK. 05.03.019

PENGESAHAN PENGUJI

GAMBARAN KADAR HEMOGLOBIN PADA REMAJA *GAMER* PRIA
LITERATUR REVIEW

Disusun Oleh :

Nurul Ika Inshani

Telah dipertahankan di depan dewan penguji pada tanggal dan dinyatakan telah memenuhi syarat

Nganjuk, 11 Agustus 2020

Komisi Penguji,

Lilis Majidah, S.Pd., M.Kes
NIK. 01.12.547

Ummaysaroh, S.ST
NIP. 19711206199732 006

Mengetahui,

Dr. Hariyono, S.Kep., Ns., M.Kep
NIK. 04.05.052

SURAT PERNYATAAN KEASLIAN

Yang bertanda tangan dibawah ini :

Nama : Nurul Ika Inshani

NIM : 171310069

Tempat, tanggal lahir : Nganjuk, 27 Juli 1999

Institusi : STIKes Insan Cendekia Medika Jombang

Menyatakan bahwa karya tulis ilmiah yang berjudul "GAMBARAN KADAR HEMOGLOBIN PADA REMAJA *GAMER* PRIA" adalah bukan karya tulis ilmiah milik orang lain baik sebagian maupun keseluruhan, kecuali dalam bentuk kutipan yang telah disebutkan sumbernya. Demikian surat pernyataan ini saya buat dengan sebenar-benarnya dan apabila pernyataan ini tidak benar, saya bersedia mendapat sanksi.

Nganjuk, 11 Agustus 2020

Yang menyatakan

Nurul Ika Inshani

171310069

SURAT BEBAS PLAGIASI

Yang bertanda tangan dibawah ini :

Nama : Nurul Ika Inshani

NIM : 171310069

Tempat, tanggal lahir : Nganjuk, 27 Juli 1999

Menyatakan bahwa karya tulis ilmiah yang berjudul "GAMBARAN KADAR HEMOGLOBIN PADA REMAJA *GAMER* PRIA" adalah bukan karya tulis ilmiah milik orang lain baik sebagian maupun keseluruhan, kecuali dalam bentuk kutipan yang telah disebutkan sumbernya. Demikian surat pernyataan ini saya buat dengan sebenar-benarnya dan apabila pernyataan ini tidak benar, saya bersedia mendapat sanksi.

Nganjuk, 11 Agustus 2020

Yang menyatakan

Nurul Ika Inshani

171310069

RIWAYAT HIDUP

Penulis dilahirkan di Nganjuk, 27 Juli 1999 dari pasangan bapak Sugeng Budiono dan Suparti. Penulis merupakan putri pertama dari dua bersaudara. Tahun 2011 Penulis lulus dari SDN Sekaran 1. Tahun 2014 penulis lulus dari SMPN 2 Nganjuk. Pada Tahun 2017 penulis lulus dari SMAN 3 Nganjuk. Pada tahun 2017 penulis lulus seleksi masuk STIKes "Insan Cendekia Medika Jombang " jalur Undangan. Penulis memilih program studi D-III Analis Teknologi Laboratorium Medik dari pilihan program studi yang ada di STIKes "Insan Cendekia Medika Jombang ".

Nganjuk, 11 Agustus 2020

Yang menyatakan

Nurul Ika Inshani
171310069

MOTTO

"Allah selalu bersama orang-orang yang sabar (Qs. Al-Anfal : 66)"

KATA PENGANTAR

Puji syukur kehadirat Allah SWT yang telah melimpahkan rahmat dan karunia-Nya sehingga Karya Tulis Ilmiah dengan judul “Kadar Hemoglobin pada Remaja Gamer Pria” berhasil diselesaikan dengan tepat waktu.

Karya Tulis Ilmiah ini diajukan sebagai untuk memenuhi syarat dalam menyelesaikan program pendidikan Diploma III Analis Kesehatan di STIKes Insan Cendekia Medika Jombang. Penulis menyadari, keberhasilan penyusunan Karya Tulis Ilmiah ini tidak lepas dari dukungan berbagai pihak yang sudah memberi doa, semangat dan masukan kepada penulis. Oleh karena itu,penulis ingin menghaturkan terimakasih kepada:

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Nganjuk, 04 Agustus 2020

Penulis

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Lampiran 2 : Lembar pengecekan judul
Lampiran 3 : Jurnal yang direview

BAB 1

PENDAHULUAN

1.1 Latar Belakang

Masyarakat sekarang dari tua maupun muda, saat ini sudah banyak menjadikan *game online* sebagai sarana alternatif hiburan. Sarana hiburan yang digunakan sebagian besar orang selain menonton TV dan mendengarkan musik adalah bermain *game online*. Permainan online ialah game yang bisa dimainkan oleh multi pemain lewat internet. Permainan online tidak cuma membagikan hiburan namun pula membagikan tantangan yang menarik buat dituntaskan sehingga orang bermain permainan online tanpa memperhitungkan waktu demi menggapai kepuasan (Pratiwi, 2012). Perihal ini menjadikan gamer tidak hanya pengguna permainan online namun pula bisa jadi pecandu permainan online (Pratiwi, 2012). Kecanduan permainan online yang dirasakan anak muda hendak sangat banyak menghabiskan waktunya. Anak muda menghabiskan waktu dikala bermain game lebih dari 2 jam/ hari, ataupun lebih dari 14 jam/ minggu (Rudhiati, 2015) apalagi 55 jam dalam seminggu (van Rooij, 2011).

Menurut (Kuss, D.J , 2011) sebagian tahun terakhir, riset tentang kecanduan permainan online sudah bertambah baik dalam kuantitas ataupun mutu. Riset awal mengatakan kalau permainan/game online ialah permasalahan untuk pelajar.

(Kuss, D.J , 2011) menyatakan bahwa kecanduan permainan online di masa dikala ini memberitahukan ditaksir prevalensi kecanduan permainan online semakin bertambah di dunia. Di negara-negara Asia Tenggara, akibat negatif dari kecanduan permainan online sudah menimbulkan pemerintah serta penyedia layanan kesehatan menjadikan permasalahan yang sungguh-sungguh serta berupaya untuk membuat peningkatan pada serangkaian inisiatif buat menghalangi serta menanggulangi permasalahan tersebut.

Bagi Asosiasi Penyelenggara Jasa Internet Indonesia(APJII)(2018) kalau sebanyak 17, 1% internet digunakan untuk permainan online. Indonesia memiliki jumlah pemain permainan yang lumayan besar (Nabila, 2019). Tetapi disebabkan keterbatasan informasi hasil riset perihal ini jumlah pemain permainan di STIKes Insan Cendekia Medika Jombang belum diketahui secara cepat.

Hasil studi pendahuluan pada peneliti yang dilakukan tanggal 19 Maret 2020 bahwa dilakukan wawancara terhadap 4 remaja *gamer* bagaimana pola tidur maupun intensitas bermain *game* pada remaja tersebut. Setelah wawancara, dilakukan pemeriksaan kadar hemoglobin pada 4 remaja *gamer* pria dimana kadar hemoglobin pada 3 remaja *gamer* pria hasilnya dibawah normal sedangkan kadar hemoglobin pada 1 remaja *gamer* pria hasilnya normal. Penurunan kadar hemoglobin inilah yang dapat menyebabkan penyakit anemia.

Menurut Rendi (Sinanto, 2019) bahwa kegiatan bermain permainan online yang dicoba secara kelewatan bisa membawa pengaruh negatif pada anak. Akibat negatif yang diartikan merupakan berkurangnya jam tidur serta pergantian pola tidurnya. Selain itu, aktivitas fisik berlebihan dan tidur kurang dari delapan jam kurang baik terhadap kesehatan. Pola tidur yang kurang baik bisa menimbulkan penurunan kadar hemoglobin darah. Penurunan hemoglobin ini bisa menimbulkan penyakit yaitu anemia. Terkait dengan kecanduan bermain *game* pada orang yang sering bermain *game* adalah sebuah kebiasaan yang kurang baik, karena kecanduan tersebut membuat individu tidak dapat mengontrol diri, dalam hal ini adalah mengelola pola istirahat tidur yang baik.

Gamer biasanya tidak dapat mengendalikan diri pada pola tidur di malam hari. Pada waktu tidur, suplai oksigen oleh darah ke otak akan menurun. Darah ialah salah satu jaringan dalam tubuh yang berupa cair bercorak merah. Karena sifat darah yang berbeda dengan jaringan lain, menyebabkan darah bisa bergerak dari satu tempat ke tempat lain sehingga bisa menyebar ke bermacam kompartemen badan. Darah mengangkut oksigen dari paru ke jaringan yang terbentuk selama metabolisme jaringan ke paru. Sehubungan dengan pengangkutan oksigen dan karbondioksida dalam tubuh manusia dilakukan oleh darah, maka dalam hal ini yang berperan adalah hemoglobin.

Hemoglobin(Hb ataupun HGB) ialah protein yang mengikat besi(Fe^{2+}) bagaikan komponen utama dalam eritrosit yang berfungsi transportasi O_2 serta CO_2 dan memberikan warna merah pada darah (Gilang, 2017). Pada sel darah merah, hemoglobin berjumlah sangat besar. Apabila jumlah hemoglobin dalam sel darah merah sangat sedikit, maka orang akan terlihat pucat dimana keadaan ini disebut anemia. Jika sel darah merah kekurangan hemoglobin, maka suplai oksigen ke dalam jaringan tubuh akan berkurang. Sehingga menyebabkan proses metabolisme dalam tubuh mengalami gangguan.

Berdasarkan masalah tersebut perlu dilakukan pemeriksaan kadar hemoglobin pada *gamer*. Individu *gamer* tersebut mempunyai waktu tidur yang kurang pada malam hari dan pola tidur yang tidak teratur. Kurang nya waktu tidur tersebut bisa menyebabkan penurunan kadar hemoglobin pada tubuh. Maka, perlunya dilakukan penelitian pada *gamer* terhadap pemeriksaan kadar hemoglobin. Selain itu pola istirahat yang memenuhi atau cukup, minum air yang memenuhi kebutuhan tubuh, makan makanan bergizi perlu diperhatikan agar tidak terjadi penurunan hemoglobin dalam darah.

1.2 Rumusan Masalah

Bagaimana Gambaran Kadar Hemoglobin pada Remaja *Gamer* Pria ?

1.3 Tujuan

Untuk Mengetahui tentang Gambaran Kadar Hemoglobin pada Remaja *Gamer* Pria.

1.4 Manfaat

Manfaat teoritis yaitu diharapkan dapat menambah keilmuan terhadap pengaruh kadar hemoglobin pada seorang gamer dimana dapat menyebabkan penurunan kadar hemoglobin yang dapat menyebabkan penyakit anemia.

Manfaat praktis yaitu dapat memberikan informasi tentang kadar hemoglobin pada gamer sehingga dapat meningkatkan kesadaran untuk selalu menjaga pola tidur dan istirahat yang cukup agar terhindar dari penurunan hemoglobin yang bisa menyebabkan penyakit anemia.

BAB 2

TINJAUAN PUSTAKA

2.1 Hemoglobin

2.1.1 Pengertian Hb (Hemoglobin)

Hemoglobin berasal dari kata yakni '*hemos*' yang artinya darah dan '*globin*' yang artinya protein. Hemoglobin adalah suatu komplek heme dengan proteiin tetramer yang dibentuk dari dua pasang sub unit polipeptida. Hemoglobin secara alamiah ialah suatu pigmen yang berwarna, oleh karena itu hemoglobin akan tampak berwarna kemerahan apabila berikatan dengan O_2 dan berwarna kebiruan apabila mengalami deoksigenasi (Danico, 2015).

Hemoglobin (Hb ataupun HGB) ialah protein yang mengikat besi (Fe2+) sebagai komponen utama dalam eritrosit yang berfungsi untuk transportasi O_2 serta CO_2 dan memberikan corak/warna merah pada darah. Tiap heme dalam Hb berikatan dengan O_2, hingga Hb disebut oksihemoglobin (HbO2) (Gilang, 2017).

Hemoglobin ialah komponen berarti dari sel darah merah yang mempunyai kedudukan dalam transportasi O_2 serta CO_2. Hemoglobin membagikan melamin natural pada sel darah merah. Zat besi yang ada di hemoglobin, pada saat berikatan dengan oksigen akan nampak kemerahan. Sebaliknya bila zat besi tersebut berikatan dengan karbon dioksida akan berganti warna keunguan (Sherwood, 2012).

2.1.2 Struktur Hemoglobin

Molekul hemoglobin terdiri dari 2 struktur utama ialah heme serta globin, dan terdapat struktur tambahan, yaitu :

a. Heme

Struktur ini melibatkan 4 atom besi dalam wujud Fe3+ dikelilingi oleh cincin protoporfirin IX, sebab zat besi dalam wujud Fe3+ tidak bisa mengikat oksigen. Protoporfirin IX merupakan produk akhir dalam sintesis molekul heme. Besi bergabung dengan protoporfirin untuk membentuk heme molekul yang lengkap (Kiswari, 2014).

b. Globin

Terdiri dari asam amino yang menghubungkan serta membentuk rantai polipeptida. Hemoglobin berusia/dewasa terdiri atas alfa serta rantai beta. Rantai alfa mempunyai 141 asam amino, sebaliknya rantai beta mempunyai 146 rantai asam amino. Heme serta globin dari molekul hemoglobin dihubungkan oleh ikatan kimia (Kiswari, 2014).

c. Struktur tambahan

Struktur tambahan yang menunjang molekul hemoglobin merupakan 2, 3- difosfogliserat (2, 3- DPG), sesuatu zat yang dihasilkan lewat jalan Embden-Meyerhof yang anaerob sepanjang proses glikolisis. Struktur ini berhubungan erat dengan afinitas oksigen dari hemoglobin (Kiswari, 2014).

2.1.3 Pembentukan Hemoglobin

Pembentukan hemoglobin terjadi pada sumsum tulang melewati stadium pematangan. Sel darah merah memasuki sirkulasi sebagai retikulosit dari sumsum tulang. Beberapa kecil hemoglobin masih dihasilkan sepanjang 24- 48 jam pematangan. Waktu sel darah merah menua, sel ini jadi lebih kaku serta lebih rapuh, kesimpulannya rusak. Hemoglobin paling utama di fagositosis limfa, hati serta sumsum tulang setelah itu direduksi jadi heme serta globin, globin masuk kembali ke dalam sumber asam amino. Besi dibebaskan dari hem serta sebagian besar diangkut oleh plasma transferin ke sumsum tulang buat pembuatan sel darah merah baru (Sadikin, 2014).

2.1.4 Fungsi Hemoglobin

Hemoglobin berperan sebagai transportasi oksigen (O_2) serta karbondioksida (CO_2). Selain itu, fungsi utama hemoglobin yaitu untuk mengangkut O_2 dari paru- paru, dan mampu menarik CO_2 dari jaringan, serta menjaga pH darah dalam keadaan seimbang (Kiswari, 2014).

2.1.5 Derivat Hemoglobin

Derivat- derivat hemoglobin terdiri dari:

a. Methemoglobin (Hi)

Methemoglobin (Hi) merupakan turunan dari Hb, dimana besi ferro teroksidasi menjadi besi ferri. Seorang individu normal memiliki methemoglobin mencapai 1,5% (Kiswari, 2014).

b. Sulfhemoglobin (SHb)

Sulfhemoglobin merupakan campuran dari hasil oksidasi. Tidak seperti methemoglobin, sulfhemoglobin tidak dapat berkurang, dan tetap berada di dalam sel sampai merusak (Kiswari, 2014).

c. Karboksihemoglobin (HbCO)

Hb memiliki kapasitas untuk bergabung dengan CO dengan afinitas 210 kali lebih besar pada O^2 (Kiswari, 2014).

2.2 Kadar Hb (Hemoglobin)

2.2.1 Pengertian Kadar Hb (Hemoglobin)

Kadar Hb (hemoglobin) adalah konsentrasi Hb (hemoglobin) dalam pembuluh darah. Pemeriksaan kadar Hb ini merupakan uji laboratorium yang sering di periksa/dilakukan. Kekurangan Hb dalam darah menyebabkan minimnya oksigen yang diedarkan keseluruh tubuh ataupun otak, sehingga memunculkan indikasi lesu, lelah, letih, serta lemah Pemeriksaan kadar Hb ini adalah salah satu cara paling sering sebagai skrining penyakit anemia.

2.2.2 Faktor-faktor yang Mempengaruhi Kadar Hb (Hemoglobin)

1. Pola makan

Untuk melindungi kadar hemoglobin tetap normal, dibutuhkan konsumsi yang bisa memenuhi kebutuhan zat besi. Zat besi ada pada makanan yang bersumber dari hewan ataupun tanaman/tumbuhan. Sebagian tipe makanan mempunyai kandungan zat besi yang besar semacam bayam merah, beras merah, hati sapi, kacang hijau, kacang merah, kedelai, kerang, oncom, telur bebek, tempe, ikan salmon serta tuna. Sumber makanan tersebut memiliki 4 miligram zat besi per 100 gr. Tidak hanya zat besi, vit B12 pula merupakan salah satu komponen sangat penting dalam pembuatan hemoglobin (Sherwood, 2012).

2. Style/gaya hidup

Teman sekitar dan kehidupan sosial dapat mendorong pergantian gaya hidup seperti asupan makanan maupun kegiatan/aktivitas. Anak muda/remaja kerap memastikan sendiri makanan yang di konsumsi. Biasanya remaja/anak muda lebih suka makanan jajanan yang kurang bergizi semacam gorengan, coklat, permen serta es. Style/gaya hidup tersebut mempengaruhi konsumsi yang diperoleh remaja/anak muda sebab konsumsi makanan yang tidak seimbang (Proverawati, 2011).

3. Kecukupan Fe dalam tubuh

Fe (Besi) diperlukan untuk memproduksi Hb, sehingga anemia gizi besi akan menimbulkan terjadinya sel darah merah yang lebih kecil serta kandungan hemoglobin yang rendah. Besi berfungsi dalam sintesis Hb dalam sel darah merah serta mioglobin dalam sel otot (Lyza, 2010).

4. Metabolisme Fe dalam tubuh

Terdapat 2 bagian Fe dalam tubuh, ialah bagian fungsional yang dipakai untuk keperluan metabolisme serta bagian yang merupakan cadangan. Hemoglobin, sitokrom, mioglobin, dan enzim hem serta nonhem merupakan wujud besi fungsional serta berjumlah antara 25-55 miligram/kilogram berat tubuh. Sedangkakan Fe cadangan apabila diperlukan untuk fungsi-fungsi fisiologis serta berjumlah 5-25 miligram/kilogram berat tubuh. Ferritin serta hemosiderin merupakan wujud Fe cadangan yang umumnya ada dalam hati, limpa serta sumsum tulang. Metabolisme Fe dalam tubuh terdiri dari proses absorpsi, pengangkutan, pemanfaatan, penyimpanan serta pengeluaran (Lyza, 2010).

5. Kebiasaan merokok

Merokok ialah salah satu aspek penting yang dapat mempengaruhi kandungan hemoglobin. Rokok memiliki banyak zat beracun serta komponen yang menimbulkan kanker dan beresiko untuk kesehatan, semacam nikotin, nitrogen oksida, CO, hidrogen sianida serta radikal (Adiwijayanti, 2015).

6. Pola tidur yang kurang/tidak teratur

Gamer umumnya tidak dapat mengendalikan diri pada pola tidur di malam hari. Pada waktu tidur, suplai oksigen oleh darah ke otak akan menurun. Darah ialah salah satu jaringan dalam tubuh yang berupa cairan bercorak merah. Sebab sifat darah yang berbeda dengan jaringan lain, dapat menyebabkan darah bisa bergerak dari satu tempat ke tempat lain sehingga bisa menyebar ke bermacam kompartemen tubuh (Gilang, 2017). Sehubungan dengan pengangkutan oksigen serta karbondioksida dalam tubuh manusia dilakukan oleh darah, maka hal ini yang berperan ialah hemoglobin.

7. Jenis kelamin

Dalam kondisi normal, pria mempunyai kandungan hemoglobin lebih tinggi daripada wanita. Perihal ini dipengaruhi oleh fungsi fisiologis serta metabolisme pria yang lebih aktif daripada wanita. Kandungan hemoglobin wanita lebih gampang turun, sebab menghadapi siklus haid yang teratur tiap bulannya. Ketika wanita menghadapi haid biasanya banyak kehabisan zat besi, oleh sebab itu kebutuhan zat besi pada wanita lebih banyak daripada pria (Adiwijayanti, 2015).

2.2.3 Metode Pemeriksaan Kadar Hb (Hemoglobin)

Terdapat beberapa metode pemeriksaan Hb (hemoglobin), yaitu :

1. Metode Tallquist

   Dengan menyamakan darah asli dengan suatu skala warna/corak yang bergradasi mulai dari warna/corak merah muda hingga warna/corak merah tua (10- 100%). Metode tallquist saat ini telah ditinggalkan sebab tingkatan kesalahannya dapat mencapai 30- 50% (Kiswari, 2014).

2. Metode Cu-Sulfat

   Metode ini digunakan untuk menetapkan kandungan hemoglobin, biasanya digunakan untuk mendapatkan donor yang cocok (Kiswari, 2014).

3. Metode Sahli

   Metode ini ialah suatu metode dalam penetapan Hb secara visual. Untuk menentukan kadar Hb yaitu dilakukan dengan cara mengencerkan kombinasi larutan tersebut dengan aquadest hingga warnanya sama dengan warna standart di tabung reaksi (Kiswari, 2014).

4. Metode Cyanmethemoglobin

Metode ini mempunyai keuntungan, ialah kenyamanan serta standart, dimana larutan ini cukup stabil dan mudah didapat. Darah diencerkan dalam larutan kalium sianida serta ferri sianida. Absorbansi larutan diukur dengan spektrofotometer pada panjang gelombang 540 nm serta dibandingkan dengan larutan standart HiCN (Kiswari, 2014)

5. Oksihemoglobin (HbO_2)

   Metode ini merupakan metode yang sangat simpel serta sangat cepat yang menggunakan fotometer. Kerugiannya ialah tidak memungkinkan untuk mempersiapkan HbO2 dalam kondisi normal/stabil, sehingga kalibrasi terhadap perlengkapan wajib dilakukan secara tertib menggunakan larutan HiCN ataupun standart sekunder darah (Kiswari, 2014).

6. Metode Hematology Analyzer

   Hematology analyzer merupakan perlengkapan untuk mengukur sampel berupa darah. Hematology Analyzer digunakan untuk mengecek darah lengkap dengan tata cara mengukur serta menghitung sel darah dengan tata cara otomatis bersumber pada impedansi aliran listrik ataupun berkas sinar terhadap sel-sel yang dilalui. Tidak hanya itu alat ini dapat digunakan untuk pengecekan hematologi rutin yang meliputi hitung sel leukosit, hitung jumlah sel trombosit serta pengecekan hemoglobin.

2.3 *Gamer*

2.3.1 Pengertian *Gamer*

Menurut kamus Cambridge daring, *gamer* memiliki arti *"Someone who likes playing computer games"*. Jika diterjemahkan menjadi "seseorang yang senang bermain *game* komputer (elektronik)". Jadi, seseorang dapat bisa dikatakan sebagai *gamer* jika dia menyukai *game* atau suka bermain *game*, tak peduli seberapa besar wawasannya tentang *game*, koleksi *game*, atau kemampuan dalam bermain (Jatmika, 2016).

2.3.2 Kecanduan *Game*/Permainan *Online*

World Health Organization (WHO, 2018) mendefinisikan kecanduan *game*/permainan *online* bagaikan kendala mental yang dimasukkan ke dalam International Classification of Disease (ICD-11) Perihal ini ditandai dengan kendala kontrol atas permainan dengan meningkatnya prioritas yang diberikan pada permainan lebih dari aktivitas lain. Sikap tersebut terus dilanjutkan meski membagikan konsekuensi negatif pada dirinya. Suatu riset menampilkan bahwa kecanduan *game*/permainan *online* lebih sering terjadi pada remaja/anak muda (Brand, 2017).

Kecanduan bermain *game*/permainan secara berlebihan dikenal dengan *Game Addiction*, yang bisa diartikan yaitu seorang anak seakan-akan tidak ada hal-hal yang mau dikerjakan selain bermain *game*, serta seolah-olah *game*/permainan ini merupakan hidupnya (Dlugoz, 2012).

Kecanduan *game/*permainan *online* yang dirasakan remaja/anak muda sangat banyak menghabiskan waktunya. Remaja/anak muda menghabiskan waktu dikala bermain *game*/permainan lebih dari 2 jam/ hari, ataupun lebih dari 14 jam/ minggu (Rudhiati, 2015) apalagi 55 jam dalam seminggu (van Rooij, 2011).

2.3.3 Dampak Kecanduan *Game Online*

Kecanduan *game*/permainan *online* bisa memiliki dampak negatif ataupun bahaya untuk remaja/anak muda yang mengalaminya. Akibat dari kecanduan *game/*permainan *online* yaitu meliputi 5 aspek, antara lain aspek kesehatan, aspek psikologis, aspek akademik, aspek sosial, serta aspek keuangan (King, 2018).

1. Aspek Kesehatan

   Kecanduan *game*/permainan *online* menyebabkan kesehatan remaja/anak muda menurun. Remaja/anak muda yang kecanduan game/permainan online akan memiliki imunitas yang lemah akibat kurang waktu tidur, sering terlambat makan, serta kurangnya aktivitas fisik (Männikkö, 2015).

2. Aspek Akademik

   Game/permainan *online* dapat menguurangi kegiatan yang positive dimana sepatutnya dijalani anak pada umur pertumbuhan mereka. Anak yang mengalami kecanduan pada permainan dapat mempengaruhi motivasi belajar sehingga dapat mengurangi waktu belajar serta bersosialisasi dengan teman-teman mereka.

3. Aspek Sosial

   Remaja/anak muda yang terbiasa hidup di dunia maya, biasanya kesusahan saat bersosialisasi di dunia nyata. Perilaku antisosial, tidak mempunyai kemauan untuk berbaur dengan warga/masyarakat, keluarga smaupun teman merupakan identitas yang ditunjukkan remaja/anak muda yang kecanduan game/permainan online (Sandy, 2019)

2.3.4 Pengaruh Kadar Hemoglobin pada Remaja Gamer Pria Terhadap Pola Tidur yang Tidak Teratur

Menurut Rendi (Sinanto, 2019) bahwa aktivitas bermain *game/*permainan *online* yang dilakukan secara berlebihan dapat berdampak negatif pada anak. Dampak negatif ini adalah berkurangnya jam tidur dan perubahan pola tidurnya. Selain itu, aktivitas fisik berlebihan dan tidur kurang dari delapan jam kurang baik terhadap kesehatan. Pola tidur yang kurang baik dapat menyebabkan penurunan kadar Hb/hemoglobin darah. Penurunan hemoglobin ini dapat menyebabkan penyakit yaitu anemia. Terkait dengan kecanduan bermain *game* pada orang yang sering bermain *game* adalah sebuah kebiasaan yang kurang baik, karena kecanduan tersebut membuat individu tidak dapat mengontrol diri, dalam hal ini adalah mengelola pola istirahat tidur yang baik.

Penelitian Goh Matsuda dan Kazuo Hiraki (2006) menyatakan bahwa mayoritas anak-anak menampilkan penurunan oxyHb terkait game di DPFC. *Game*-related penurunan oxyHb juga sebelumnya diamati pada subjek dewasa. Sebagian besar anak-anak menampilkan oxyHb terkait permainan penurunan DPFC. Hanya sebagian kecil anak-anak yang menunjukkan oxyHb meningkat untuk kedua kategori game. Hanya 2 dari 10 anak (G. Matsuda, 2006).

BAB 3

METODE PENELITIAN

3.1 Strategi dan Pencarian Literatur

3.1.1 Framework yang Digunakan

Strategi yang digunakan untuk mencari artikel yaitu menggunakan PICOS *framework*.

a. P *(Population/problem)*, populasi atau masalah yang akan di analisis
b. I *(Intervention)*, suatu tindakan penatalaksanaan terhadap kasus perorangan atau masyarakat serta pemaparan tentang penatalaksanaan.
c. C *(Comparation)*, penatalaksanaan lain yang digunakan sebagai pembanding
d. O *(Outcome)*, hasil atau luaran yang diperoleh pada penelitian
e. S *(Study design)*, desain penelitian yang digunakan yaitu dari jurnal yang akan di review.

3.1.2 Kata Kunci yang digunakan

Pencarian jurnal atau artikel ini menggunakan kata kunci dimana kata kunci ini digunakan untuk menspesifikasikan atau memperluas pencarian, hal ini agar mempermudah dalam menentukan jurnal atau artikel yang digunakan. Kata kunci untuk jurnal yang digunakan untuk penelitian ini adalah "*Gaming/game*" AND "*Hemoglobin*".

3.1.3 Database atau Search Engine yang Digunakan

Penelitian ini menggunakan data sekunder dimana data sekunder ini diperoleh bukan dari pengamatan langsung, tetapi diperoleh dari hasil penelitian yang telah dilakukan oleh peneliti-peneliti terdahulu. Sumber data sekunder yang didapat berupa jurnal atau artikel yang relevan dengan topik menggunakan database yaitu melalui *Semantic Scholar*, *ResearchGate*, dan *Science Direct.*

3.2 Kriteria Inklusi dan Eksklusi

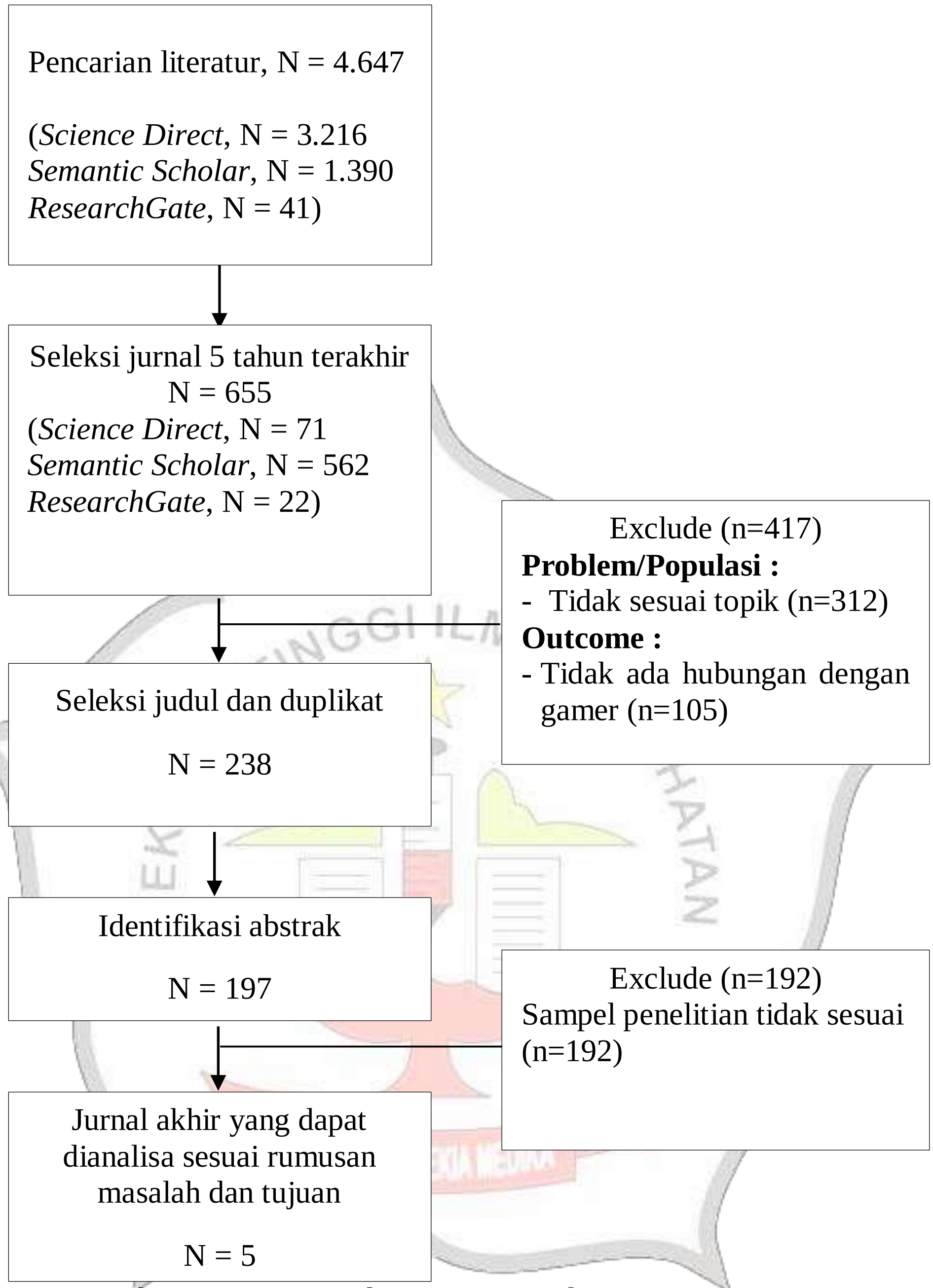
Kriteria	Inklusi	Eksklusi
Population/problem	Jurnal nasional dan international yang berhubungan dengan topik penelitian yakni kadar hemoglobin pada remaja gamer pria	Jurnal nasional dan internasional yang menyimpang jauh dengan topik penelitian
Intervention	Tidak ada intervention	Ada Intervention
Comparation	Tidak ada faktor pembanding	Ada faktor pembanding
Outcome	Kadar hemoglobin pada remaja *gamer* pria	Selain kadar hemoglobin pada remaja *gamer* pria
Study Design	*cross sectional*	Eksperimental
Tahun Terbit	Artikel atau jurnal yang terbit pada tahun 2006 dan setelah tahun 2014	Artikel atau jurnal yang terbit sebelum tahun 2014
Bahasa	Bahasa Indonesia dan bahasa Inggris	Bahasa Korea, bahasa Thailand, bahasa China

Tabel 3.2 Kriteria inklusi dan eksklusi dengan format PICOS

3.3 Seleksi Studi dan Penilaian Kualitas

3.3.1 Hasil Pencarian dan Seleksi Studi

Berdasarkan penelitian terkait kadar hemoglobin pada remaja gamer pria, suatu jurnal atau artikel sangat dibutuhkan dalam penyusunan literature review ini. Dengan publikasi *Science Direct*, *Semantic Scholar* dan *ResearcGate* yang menggunakan kata kunci "*Gaming/game*" AND "Hemoglobin" peneliti menemukan 4.647 jurnal yang sesuai dengan kata kunci tersebut, setelah itu dilakukan pemfilteran pada jurnal untuk terbitan tahun 2006 dan 2014 keatas sehingga menjadi 655. Dilakukan eliminasi pada jurnal yang tidak sesuai dan duplikasi dengan kriteria inklusi, sehingga didapatkan 5 jurnal yang akan review.



Gambar 3.3 Diagram alur review jurnal

3.3.2 Daftar Artikel Hasil Pencarian

Literature review ini menggunakan metode naratif yaitu dengan pengelompokkan data-data hasil ekstraksi yang sejenis sesuai hasil yang digunakan untuk menjawab tujuan. Jurnal penelitian yang relevan atau sesuai dengan kriteria inklusi kemudian dikumpulkan dan dibuat ringkasan jurnal yang meliputi nama peneliti, tahun terbit, volume jurnal, judul jurnal, Metode penelitian pada jurnal, hasil penelitian dan database.

No	Author	Tahun	Volume, angka	Judul	Metode (Desain, Sampling, Variabel, Instrumen, Analisis)	Hasil penelitian	Database
1.	Goh Matsuda and Kazuo Hiraki	2006	Vol.29 , No.2	*Sustained decrease in oxygenated hemoglobin during video games in the dorsal prefrontal cortex: A NIRS study of children*	D : *Cross sectional* S : *Simple random sampling* V : Penurunan hemoglobin teroksigenasi I : NIRS *(near infrared spectrocopy)* A : Statistik inferensial	Hasil penelitian tersebut menyatakan bahwa mayoritas anak-anak menampilkan penurunan oxyHb terkait game di DPFC. Game-related penurunan oxyHb juga sebelumnya diamati pada subjek dewasa	*Scient Direct*
2.	Li, Yue Zhang, Lei Long, Kehong Gong, Hui Lei, Hao	2018	Vol.11, No.9	*Real-time monitoring prefrontal activities during online video game playing by functional near-infrared spectroscopy*	D : *Cross sectional* S : *Simple random sampling* V : Pemantauan real-time kegiatana prefontal saat bermain video game online I : NIRS *(near infrared spectrocopy)* A : Statistik inferensial	Hasil penelitian tersebut menyatakan bahwa selama bermain LOL, permulaan game, pertemuan pertama dengan juara musuh, serta game tertentu peristiwa seperti Bunuh, Bantu dan Bunuh, bisa membangkitkan respons HbO2 / Hb yang dikunci waktu spesifik dalam PFC. Aktivitas prefrontal yang terkait dengan online bermain video game menunjukkan	*Research Gate*

						kesamaan dengan dan perbedaan dari yang diamati selama visuomotor laboratorium tugas.	
3.	Witte, Matthias Ninaus, Manuel Kober, Silvia Erika Neuper, Christa Wood, Guilherme	2015	Vol.10, No.8	*Neuronal correlates of cognitive control during gaming revealed by near-infrared spectroscopy*	D : *Cross sectional* S :*Simple random sampling* V : Korelasi neuronal dari kontrol kodnitif selama permainan I : NIRS *(near infrared spectrocopy)* A : Statistik inferensial	Hasil penelitian tersebut menyatakan bahwa tuntunan berbeda pada kontrol kognitif selama bermain game tercermin dalam perubahan konsentrasi hemoglobin yang dicatat dengan NIRS. Peningkatan reaktivitas sinyal NIRS pada area yang terdistribusi.	*Research Gate*
4	Fujiki, Ryo Morita, Kiichiro Sato, Mamoru Yamashita, Yuji Kato, Yusuke Ishii, Yohei Shoji, Yoshihisa Uchimura, Naohisa	2014	Vol.10	*Single event-related changes in cerebral oxygenated hemoglobin using word game in schizophrenia*	D : *Cross sectional* S :*Cluster random sampling* V : Perubahan tunggal yang berhubungan dengan peristiwa dalam hemoglobin beroksigen serebral I : NIRS *(near infrared spectrocopy)* A : Statistik inferensial	Hasil penelitian tersebut menyatakan bahwa aktivitas PFC berkurang dan positif secara signifikan antara perubahan oxy-Hb dan gejala psikiatri positif skor pada pasien dengan skizofrenia.	*Research Gate*

5	Ouankhamchan, Phetnidda Fujinami, Tsutomu	2015	Vol,10	*Effects of Casual Computer Game on Cognitive performance through Hemodynamic Signals*	D : *Cross sectional* S : *Simple random sampling* V:Pengaruh Game Komputer Santai pada Kinerja Kognitif I : NIRS *(near infrared spectrocopy)* A : Statistik inferensial	Hasil penelitian tersebut menyatakan bahwa permainan puzzle casaul dalam bentuk versi komputer meningkatkan kapasitas langsung dari fleksibilitas kognitif dan kemampuan visio-spasial, namun demikian memori jangka pendek dan kapasitas mata cepat masih dalam ambiguitas. Selain itu, fitur yang diselidiki seperti median max-min normalized oxyHb dan kekuatan spektral densitas sinyal hemoglobin beroksigen menunjukkan perbedaan aktivasi otak di mana sinyal oxy-Hb setelah permainan kasual memiliki variasi yang lebih kecil dibandingkan dengan sebelum permainan kasual	*Semantic Scholar*

BAB 4

HASIL DAN PEMBAHASAN

4.1 Hasil

Tabel 4.1 Karakteristik umum dalam menyeleksi studi

No	Kategori	N	%
A	**Tahun publikasi**		
1	2006	1	20
2	2014	1	20
3	2015	2	40
4	2018	1	20
	Total		**100**
B	**Bahasa**		
1	Bahasa Inggris	5	100
	Total		
C	**Database**		**100**
1	Science direct	1	20
2	Semantic Scholar	1	20
3	ResearchGate	3	60
	Total		**100**
D	**Design penelitian**		
1	Cross sectional	5	100
	Total		**100**

Tabel 4.2 Persamaan dan perbedaan jurnal yang direview

Referensi	Persamaan	Perbedaan
Goh Matsuda et al, 2006	a. Jurnal meneliti hemoglobin teroksigenasi pada gamer dengan menggunakan NIRS b. Terjadi penurunan OxyHb saat bermain video game c. Design penelitian yang digunakan adalah Cross sectional d. Analisis yang digunakan adalah analisis statistik inferensial	a. Menggunakan metode simple random sampling b. Subjek yang diteliti yaitu Dua puluh anak Jepang yang sehat (15 laki-laki dan 5 perempuan, usia 7 sampai 14 tahun) kecuali satu laki-laki (kidal)

	e. Instrumen penelitian menggunakan NIRS (near infrared spectrocopy)	
Li et al, 2018	a. Jurnal meneliti hemoglobin teroksigenasi pada gamer dengan menggunakan NIRS b. Terjadi penurunan OxyHb saat bermain video game c. Design penelitian yang digunakan adalah Cross sectional d. Analisis yang digunakan adalah analisis statistik inferensial e. Instrumen penelitian menggunakan NIRS (near infrared spectrocopy)	a. Menggunakan metode simple random sampling b. Subjek yang diteliti yaitu mahasiswa biasa yang direkrut di kampus, semua dalam kondisi fisik dan mental yang baik dan memiliki penglihatan normal yang normal atau terkoreksi
Witte et al, 2015	a. Jurnal meneliti hemoglobin teroksigenasi pada gamer dengan menggunakan NIRS b. Terjadi penurunan OxyHb saat bermain video game c. Design penelitian yang digunakan adalah Cross sectional d. Analisis yang digunakan adalah analisis statistik inferensial e. Instrumen penelitian menggunakan NIRS (near infrared spectrocopy)	a. Menggunakana metode simple random sampling b. Enam belas orang dewasa yang sehat (9 perempuan, 7 laki-laki, usia rata-rata 23 ± 2 tahun)
Fujiki et al, 2014	a. Jurnal meneliti hemoglobin teroksigenasi pada	a. Menggunakan metode cluster random sampling

	gamer dengan menggunakan NIRS b. Terjadi penurunan OxyHb saat bermain video game c. Design penelitian yang digunakan adalah Cross sectional d. Analisis yang digunakan adalah analisis statistik inferensial e. Instrumen penelitian menggunakan NIRS (near infrared spectrocopy)	b. 35 pasien rawat jalan dengan skizofrenia (19 pria dan 16 wanita; usia rata-rata, 29,4 ± 5,8 tahun, tipe paranoid) dan jumlah subyek kontrol sehat yang sama (19 pria dan 16 wanita; usia rata-rata, 27,6 ± 6,8 tahun)
Ouankhamchan et al, 2015	a. Jurnal meneliti hemoglobin teroksigenasi pada gamer dengan menggunakan NIRS b. Terjadi penurunan OxyHb saat bermain game c. Design penelitian yang digunakan adalah Cross sectional d. Analisis yang digunakan adalah analisis statistik inferensial e. Instrumen penelitian menggunakan NIRS (near infrared spectrocopy)	a. Menggunakan metode simple random sampling b. 7 mahasiswa di Institut Sains dan Teknologi sebagai subjek yang sehat

Tabel 4.3 Identifikasi hasil penelitian

Author	Hasil
Goh Matsuda and Kazuo Hiraki	a. Gambar 3 menggambarkan rasio perubahan hemodinamik yang signifikan, yaitu peningkatan, penurunan, atau tidak ada perubahan signifikan dalam konsentrasi oxyHb, di 4 wilayah selama setiap pertandingan. Secara keseluruhan, penurunan yang signifikan diamati pada 50% atau pada persentase yang lebih tinggi di setiap wilayah, kecuali di posterior kanan untuk permainan puzzle. b. Tabel 1 dan 2 . Sebagian besar anak menunjukkan penurunan DPFC terkait oxyHb. Hanya sebagian kecil anak-anak yang menunjukkan peningkatan oxyHb untuk kedua kategori game tersebut. Hanya 2 dari 10 anak, S3 dan S6, menunjukkan peningkatan oxyHb di DPFC kiri, yaitu di region kiri posterior (LP) dan anterior kiri (LA), selama pertandingan berlangsung. 8 anak yang tersisa tidak menunjukkan peningkatan oxyHb di salah satu wilayah target, meskipun penurunan oxyHb terlihat di setidaknya dua wilayah. Dua anak, S7 dan S9, menunjukkan penurunan oxyHb terutama di keempat wilayah. c. Gambar 4, rata-rata keseluruhan untuk rangkaian waktu oxyHb di wilayah RA, di mana jumlah anak tertinggi yang menunjukkan penurunan oxyHb selama kedua game, digambarkan
Li, Yue Zhang, Kehong Gong, Lei Long, Hui Lei, Hao	a. Gambar. 2. DLPFC dan FPA menunjukkan HbO yang tiba-tiba dan signifikan secara statistik 2 menurun pada permulaan game, sedangkan VLPFC memiliki HbO yang signifikan 2 meningkat (Gbr. 2B). b. Setelah permainan dimulai, konsentrasi Hb meningkat secara signifikan di DLPFC, menurun secara signifikan di VLPFC, tetapi tidak memiliki perubahan signifikan pada FPA (Gbr. 2C). c. HbO 2 tingkat di FPA tetap di bawah baseline setelah pertemuan pertama, disertai dengan bertahap penurunan tingkat Hb (Gbr. 2B dan C). d. Musuh pertama pertemuan juara membangkitkan HbO lebih lanjut 2 meningkat dan Hb menurun di VLPFC, dan perubahan seperti itu cenderung level off sekitar 100 detik setelah pertemuan (Gbr. 2A-C). e. Gambar 3 menampilkan pemetaan topografi

	yang dirata-ratakan HbO 2 dan konsentrasi Hb selama tiga jendela waktu yang dipilih. (Gambar 4A / B dan 5). HbO relatif 2 tingkat di DLPFC memiliki undershoot pasca-acara setelah Dibunuh, yang, Namun, mulai pulih sekitar 10 detik setelah kejadian, dan mencapai level dasar pada akhir waktu 60-an f. Gambar 4C dan 5 HbO relatif 2 level di FPA tidak memiliki penurunan signifikan setelah Slain. Sebaliknya, itu tetap pada tingkat dasar untuk jangka waktu tertentu, diikuti oleh peningkatan yang signifikan (Gambar 4C dan 5).
Witte, Matthias Ninaus, Manuel Kober, Silvia Erika Neuper, Christa Wood, Guilherme	a. Gambar 2A. Pola perubahan paling konsisten dalam sinyal NIRS di antara peserta dan saluran adalah peningkatan konsentrasi relatif oxy-Hb bersama dengan penurunan tingkat deoksi-Hb. Pada tingkat deskriptif, reaktivitas yang lebih tinggi dapat diamati untuk tugas PELAJARAN mulai dari sekitar 3 detik dari interval tugas. Rata-rata Oxy-Hb memuncak sekitar 6 hingga 8 detik, sedangkan deoxy-Hb mencapai penurunan maksimal mulai dari 8 detik. Sebaliknya, tugas ACAK dan BERLAKU dikaitkan dengan perubahan sinyal yang kurang jelas dan bertahap untuk oxy-Hb dan hampir tidak ada perubahan untuk deoxy-Hb. b. Gambar 2B. mengungkapkan bahwa peningkatan aktivasi neuron secara keseluruhan diperlukan selama tugas BELAJAR untuk menangkap objek yang jatuh. Secara khusus, peningkatan curam kurva setelah objek keenam dapat diamati bahwa jenuh untuk tiga objek terakhir saja. Sebaliknya, profil beban untuk dua tugas yang tersisa adalah serupa dan menunjukkan aktivasi yang meningkat secara bertahap. c. Gambar 3A. Plot topografi dari perbedaan Hb rata-rata yang dijelaskan secara statistik di atas menguatkan peningkatan aktivasi selama BELAJAR atas wilayah kortikal yang luas
Fujiki, Kiichiro Sato, Ryo Morita, Mamoru Yamashita, Yuji Kato, Yusuke Ishii, Yoshihisa	a. Gambar 3. korelasi antara perubahan oxy-hb dan Skor atau kinerja PaNss Perubahan Oxy-Hb di saluran kiri empat, saluran kiri tujuh, saluran kiri sepuluh, saluran kiri sebelas, saluran kanan satu, saluran kanan delapan, dan saluran kanan saluran 13 mengungkapkan korelasi positif yang

Uchimura, Yohei Shoji, Naohisa	signifikan dengan positif skor gejala pada pasien (r = 0.45, P = 0.003; r = 0.41, P = 0.007; r = 0.48, P = 0.002; r = 0,51, P = 0,001; r = 0,44, P = 0,006; r = 0,41, P = 0,008; dan r = 0,44, P = 0,005, masing-masing); Namun, tidak ada korelasi dengan negatif skor gejala (Gambar 4). Tidak ada korelasi yang ditemukan antara kinerja dan aktivasi di kedua kelompok. b. Pada pasien skizofrenia, Perubahan oxy-Hb pada setiap saluran tidak menunjukkan korelasi yang signifikan dengan durasi penyakit dan dosis obat antipsikotik. Kami menyelidiki hubungan antara aktivasi dan masing-masing obat, dan tidak menemukan apapun signifikansi statistik. Tidak ada korelasi yang signifikan antara kinerja dan skor PANSS atau IQ. Selain itu, tidak ada korelasi yang signifikan antara pengobatan dan skor PANSS atau IQ.
Ouankhamchan, Tsutomu, Phetnidda Fujinami	a. Untuk menggambarkan tingkat individu, Gambar. 5 menunjukkan nilai median oxy-Hb yang dinormalisasi dari 22 saluran fNIR untuk setiap subjek selama tugas mental melalui pengujian neurolopsikologis sebelum dan setelah memainkan permainan puzzle kausal. Hal ini ditunjukkan melalui Gambar. 5 bahwa nilai median hilang dari beberapa saluran karena intervensi kondisi fisik subjek. Dengan demikian, saluran umum yang menerima sinyal hemodinamik dengan baik dari semua subjek dianggap memantau perubahan aktivasi otak di tingkat populasi. b. Gambar 6 menunjukkan hasil yang menarik ketika semua subjek tidak termasuk subjek C mengalamipenurunan nilai tengah dari oxy-Hb yang dinormalisasi. c. Kepadatan spektral daya (PSD) sinyal oxy-Hb juga berubah secara signifikan setelah permainan kasual dimainkan. Variasi energi sinyal oxy-Hb berkurang pada pasca-sesi, khususnya, saluran 19 menunjukkan perbedaan besar dari variasi kuat oxy-Hb sebelum dan sesudah bermain game kausal.

4.2 Pembahasan

Beberapa jurnal yang berkaitan dengan kadar hemoglobin pada remaja gamer pria yang dilakukan dengan uji pemeriksaan menggunakan metode yang bermacam-macam, didapatkan hasil terjadinya penurunan hemoglobin atau OxyHb. Penurunan oxyHb dalam DPFC mungkin mencerminkan penghambatan saraf yang berasal dari permintaan perhatian untuk video permainan. Dengan demikian, bermain video game cenderung menipiskan aktivitas DPFC dibandingkan dengan istirahat, dan ini Kecenderungan umum untuk orang dewasa dan anak-anak setidaknya lebih tua dari bayi. Respons hemodinamik ini mungkin muncul dari perhatian yang menuntut untuk game video daripada dari usia subjek dan kinerja.

Penyebab penurunan oxyHb di DPFC dikarenakan video game terdiri dari banyak rangsangan seperti gambar berwarna dan suara terus menerus, tidak jelas yang konstituen dari video game menyebabkan hemodinamik tersebut mengalani perubahan dalam percobaan. Jurnal yang menyatakan mayoritas terdapat penurunan OxyHb pada anak-anak yang memainkan video game sebagian besar anak-anak menunjukkan penurunan oxyHb terkait game berkelanjutan di DPFC. Mengurangi pola oxyHb pada anak-anak selama waktu bermain video game tidak berbeda dengan orang dewasa. Tidak ada korelasi yang signifikan antara usia atau kinerja game dan perubahan oxyHb. Temuan ini menunjukkan bahwa penurunan oxyHb terkait game di DPFC adalah Fenomena umum pada orang dewasa dan anak-anak setidaknya lebih dari 7 tahun lama. Penurunan kadar hemoglobin ini juga dapat dipengaruhi karena kurangnya tidur seorang gamer pada malam hari.

Penelitian Fujiki et al, Pada pasien skizofrenia, dimana perubahan oxy-Hb pada setiap saluran tidak menunjukkan korelasi yang signifikan dengan durasi penyakit dan dosis obat antipsikotik. Dan menyelidiki hubungan antara aktivasi dan masing-masing obat, dan tidak menemukan apapun signifikansi statistik. Tidak ada korelasi yang signifikan antara kinerja dan skor PANSS atau IQ. Selain itu, tidak ada korelasi yang signifikan antara pengobatan dan skor PANSS atau IQ.

Beberapa keterbatasan pada literatur review ini terdapat perbedaan pada metode dan sampel pada tiap-tiap jurnal. Dan Terdapat beberapa literatur review yang kurang untuk menunjang data maupun hasil yang akan di review.

BAB 5

KESIMPULAN DAN SARAN

5.1 Kesimpulan

Kadar hemoglobin pada remaja gamer pria sebagian besar hemoglobin atau OxyHb nya menurun.

5.2 Saran

5.2.1 Dosen

Bagi dosen dapat digunakan dalam tugas pengabdian masyarakat untuk menginformasikan tentang pemantauan anak terhadap memainkan *game*/permainan *online* dimana dapat menyebabkan penurunan hemoglobin.

5.2.2 Orang Tua

Bagi Orang tua untuk memonitoring anak dalam memainkan sebuah *game*/ permainab *online* agar tidak terjadi kecanduan.

5.2.3 Peneliti Selanjutnya

Bagi peneliti selanjutnya untuk melakukan penelitian hal yang berbeda dalam jurnal yang direview tersebut. Dan disarankan untuk melakukan penelitian langsung karena terdapat beberapa literatur review yang kurang untuk menunjang data maupun hasil yang akan di review.

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LAMPIRAN 1

YAYASAN SAMODRA ILMU CENDEKIA
SEKOLAH TINGGI ILMU KESEHATAN
"INSAN CENDEKIA MEDIKA"
LABORATORIUM ANALIS KESEHATAN
SEKOLAH TINGGI ILMU KESEHATAN INSAN CENDEKIA MEDIKA JOMBANG
Kampus I : Jl. Kemuning 57a Candimulyo Jombag
Jl. Halmahera 33, Kaliwungu Jombang, e-Mail: Stikes_Icme_Jombang@Yahoo.Com

LEMBAR KONSULTASI

Nama : Nurul Ika Inshani
NIM : 171310069
Judul KT : Gambaran Kadar Hemoglobin pada Remaja Gamer Pria
Pembimbing I : Lilis Majidah, S.Pd.,M.kes

No.	Tanggal	Hasil Konsultasi
1.	4 Maret 2020	Konsul masalah
2.	10 Maret 2020	Konsul masalah
3.	11 Maret 2020	Konsul bab 1
4.	11 Maret 2020	Acc Bab 1
5.	02 April 2020	Konsul Bab 2 dan acc
6.	17 April 2020	Konsul Bab 3 dan 4 - Revisi kerangka konseptual - Revisi tabel definisi operasional
7.	19 April 2020	Konsul Bab 3 Kerangka konseptual
8.	21 April 2020	Konsul Bab 4 (Kerangka kerja)
9.	03 Mei 2020	Acc Bab 1-4 (Proposal KTI)
10.	23 Juli 2020	Konsul Bab 3-5
11.	23 Juli 2020	Revisi pembahasan
12.	4 Agustus 2020	Acc Pembahasan dan Acc KTI

Mengetahui,
Pembimbing Utama

Lilis Majidah, S.Pd.,M.kes

YAYASAN SAMODRA ILMU CENDEKIA
SEKOLAH TINGGI ILMU KESEHATAN
"INSAN CENDEKIA MEDIKA"
LABORATORIUM ANALIS KESEHATAN
SEKOLAH TINGGI ILMU KESEHATAN INSAN CENDEKIA MEDIKA JOMBANG
Kampus I : Jl. Kemuning 57a Candimulyo Jombag
Jl. Halmahera 33, Kaliwungu Jombang, e-Mail: Stikes_Icme_Jombang@Yahoo.Com

LEMBAR KONSULTASI

Nama : Nurul Ika Inshani
NIM : 171310069
Judul KTI : Gambaran Kadar Hemoglobin pada Remaja Gamer Pria
Pembimbing II : Ummaysaroh, S.ST

No.	Tanggal	Hasil Konsultasi
1.	04 April 2020	Konsul BAB 1 - Revisi latar belakang penelitian - Tujuan penelitian - Manfaat penelitian
2.	17 April 2020	Konsul BAB 2 - Revisi penulisan BAB - Revisi paragraf sub BAB
3.	4 Agustus 2020	Konsul BAB 3 - Revisi penulisan paragraf
4.	4 Agustus 2020	Konsul BAB 4 - Revisi urutan sub-sub BAB
5.	05 Agustus 2020	ACC KTI

Mengetahui,
Pembimbing II

Ummaysaroh, S.ST

PERPUSTAKAAN

SEKOLAH TINGGI ILMU KESEHATAN

INSAN CENDEKIA MEDIKA JOMBANG

Kampus C : Jl. Kemuning No. 57 Candimulyo Jombang Telp. 0321-865446

SURAT PERNYATAAN

Pengecekan Judul

Yang bertanda tangan di bawah ini:

Nama Lengkap : Nurul Ika Inshani

NIM : 17.131.0069

Prodi : D-III Analis Kesehatan

Tempat/Tanggal Lahir: Nganjuk/27 Juli 1999

Jenis Kelamin : Perempuan

Alamat : Ds.Sekaran, RT.04/RW.01, Kec.Loceret, Kab.Nganjuk

No.Tlp/HP : 082231802816

email : nurulika794@gmail.com

Judul Penelitian : Gambaran Kadar Hemoglobin pada Remaja Gamer Pria

Menyatakan bahwa judul LTA/Skripsi diatas telah dilakukan pengecekan, dan judul tersebut **tidak ada** dalam data sistem informasi perpustakaan. Demikian surat pernyataan ini dibuat untuk dapat dijadikan sebagai referensi kepada dosen pembimbing dalam mengajukan judul LTA/Skripsi.

Mengetahui

Ka. Perpustakaan

Dwi Nuriana, M.IP

NIK.01.08.122

LAMPIRAN 3

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NeuroImage 29 (2006) 706 – 711

Sustained decrease in oxygenated hemoglobin during video games in the dorsal prefrontal cortex: A NIRS study of children

Goh Matsuda* and Kazuo Hiraki*

Department of General Systems Studies, Graduate School of Arts and Science, The University of Tokyo, Komaba 3-8-1, Meguro-ku, Tokyo 153-8902, Japan

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Traditional neuroimaging studies have mainly focused on brain activity derived from a simple stimulus and task. Therefore, little is known about brain activity during daily operations. In this study, we investigated hemodynamic changes in the dorsal prefrontal cortex (DPFC) during video games as one of daily amusements, using near infrared spectroscopy technique. It was previously reported that oxygenated hemoglobin (oxyHb) in adults' DPFC decreased during prolonged game playing time. In the present study, we examined whether similar changes were observed in children.

Twenty children (7–14 years old) participated in our study, but only 13 of them were eventually subject to analysis. They played one or two commercially available video games; namely a fighting and a puzzle game, for 5 min. We used changes in concentration of oxyHb as an indicator of brain activity and consequently, most of the children exhibited a sustained game-related oxyHb decrease in DPFC. Decrease patterns of oxyHb in children during video game playing time did not differ from those in adults. There was no significant correlation between ages or game performances and changes in oxyHb. These findings suggest that game-related oxyHb decrease in DPFC is a common phenomenon to adults and children at least older than 7 years old, and we suggest that this probably results from attention demand from the video games rather than from subject's age and performance.

Keywords: Children; Video game; NIRS; Prefrontal cortex; Decrease

Introduction

Brain activity during a complex task corresponding to daily operations has recently attracted increasing attention (Walter et al., 2001; Calhoun et al., 2002; Hasson et al., 2004; Okamoto et al., 2004a,b). Daily operations consist of rich stimuli, and require various cognitive processing. Traditional neuroimaging studies have mainly focused on brain activity derived from a simple stimulus and task. Although brain activity during complex tasks can be inferred partially by accumulating established fundamental evidence, little is known about actual brain activity in daily life. Therefore, it is interesting to directly investigate brain activity during everyday tasks.

In the present study, we investigated prefrontal cortex activity when playing video games. A video game is one of the most popular amusements in modern life, which also involves various stimuli, and requires various cognitive functions. Because the prefrontal cortex plays an important role in many higher cognitive functions (Miller and Cohen, 2001), we speculated that a video game would activate many parts of the prefrontal cortex at first. However, our previous near infrared spectroscopy (NIRS) study with adult subjects revealed a sustained decrease of oxygenated hemoglobin (oxyHb) in DPFC during four kinds of video games (Matsuda and Hiraki, 2004). Similar results have been reported by an fMRI study using a computer driving game (Calhoun et al., 2002) and adult subjects.

The aim of this study was to examine whether similar hemodynamic changes were also detected in DPFC of children. An fMRI study of the development of spatial working memory (Thomas et al., 1999) reported that a decrease in BOLD signal in the medial superior frontal gyrus (BA 9) was observed in both adults and children. However, traditional neuroimaging studies have focused on task-related signal increases related to neural activation, while task-related signal decrease is yet, so far, to be fully discussed. Moreover, there are few neuroimaging data for children than for adults, i.e., there are only few reports available on task-related signal 'decrease' in children.

We used a near infrared spectroscopy (NIRS) technique to measure hemodynamic responses within the brain. As NIRS is non-invasive, and does not require fixing the body in a gantry like PET and fMRI, it is suitable for brain imaging studies of children. Validity of NIRS for use in a child study was proven by reports on the development of frontal function (Schroeter et al., 2004), emotion (Hoshi and Chen, 2002), and working memory (Tsujimoto et al., 2004). In addition, NIRS is a robust technique for recording with electromagnetic noise, also rendering it suitable for measurement during the use of electric devices such as video games.

* Corresponding authors. G. Matsuda is to be contacted at fax: +81 5454 4513.

E-mail addresses: matsuda@ardbeg.c.u-tokyo.ac.jp (G. Matsuda), khiraki@idea.c.u-tokyo.ac.jp (K. Hiraki).

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Materials and methods

Subjects

Twenty healthy Japanese children (15 males and 5 females, aged 7 to 14 years old) participated voluntarily in this study. All children were right-handed except for one male (left-handed). All children and their parents were informed about the purpose and

130 ms, and we then employed cumulative sampling data in 1040 ms (130 ms × 8 points) for analysis purposes.

We measured a 9 × 9 cm square area centered in the Fz of the EEG 10–20 system. A total of 16 optodes, namely eight emitters and eight detectors, were placed on the scalp alternately, and distance between optodes was set to 3 cm (Fig. 1). This recorded area corresponded to the bilateral superior frontal gyrus and middle frontal gyrus (BA 6, 8, 9, 10) (Homan et al., 1987; Okamoto et al., To increase signal-to-noise ratio, data from 24 channels were averaged into 4 regions (Fig. 2) after raw data from each channel were converted into the z-score. The z-score was calculated using the mean value and the standard deviation of oxyHb changes during the pre-task period. Consequently, mean value and standard deviation during the pre-task period were respectively changed into z-scores 0 and 1 in every channel. Although raw data of NIRS were originally relative values, and could not be averaged directly across subjects or channels, the z-score could be averaged regardless of a unit.

Sustained hemodynamic response in each region during a video game was determined individually using a correlation coefficient (r) of the individual oxyHb time series, and a 10 s delayed boxcar function. The boxcar function, which was 0 for the pre- and post-periods, and a value of 1 in the task period, was employed as a model function of hemodynamic responses, while a 10 s delay was set in order to reflect the time lag between hemodynamic response and the actual task. We interpreted that statistically significant r values ($P < 0.01$, uncorrected) indicated a task-related oxyHb increase ($r > 0$) or decrease ($r < 0$) within a target region for each subject.

Results

Fig. 3 illustrates ratios of significant hemodynamic changes, i.e., increase, decrease, or no significant change in oxyHb concentration, in 4 regions during each game. Overall, a significant decrease was observed at 50% or at a higher percentage in each region, except in the right posterior for the puzzle game.

Individual results for the correlation analysis are shown in Tables 1 and 2. Most of children displayed a game-related oxyHb decrease in DPFC. Only a minority of children showed an oxyHb increase for both game categories. Only 2 out of 10 children, S3 and S6, showed an oxyHb increase in the left DPFC, i.e., in the left posterior (LP) and the left anterior (LA) regions, during the fighting game. The remaining 8 children showed no oxyHb increase in any of the target regions, although an oxyHb decrease was apparent in at least two regions. Two children, S7 and S9, displayed an oxyHb decrease particularly in all four regions.

With the puzzle game, 3 of 8 children, S3, S5, and S6, showed an oxyHb increase in multiple regions; and S5 showed, in particular, an oxyHb increase in all four regions while the others showed a decrease or no significant change. Three of 8 children,

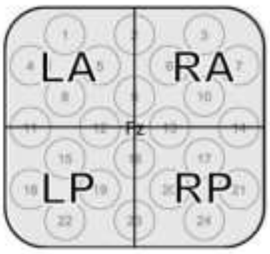

Fig. 2. The four regions used for statistical analysis. 24 channels were averaged into 4 regions. We named them LA (left anterior), RA (right anterior), LP (left posterior), and RP (right posterior), respectively. Data from channels straddled two regions, i.e., channels 2, 9, 11, 12, 13, 14, 16, and 23 were weighted at a level of 0.5 in both regions.

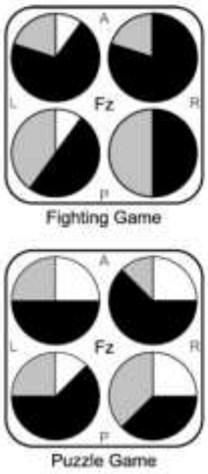

Fig. 3. Ratios of three types of hemodynamic changes. Each of the boxed pie charts corresponds topologically to the target region illustrated in Fig. 2 (upper = anterior, lower = posterior). White, black, and grey areas represent percentages of increase, decrease, and no significant change among all children involved, respectively.

S2, S9, and S12, showed a decrease in all regions while S8 exhibited neither increase nor decrease in all regions.

The grand average for the time series of oxyHb in the RA region, where the highest number of children exhibited an oxyHb decrease during both games, is depicted in Fig. 4. In both graphs, oxyHb rapidly decreased immediately after onset of the game, and subsequently rapidly recovered following the end of the game. A delay was observed between the end of the game and the point at which hemodynamic recovery commenced. Such a delayed response is assumed to reflect a time lag between task comprehension and any corresponding hemodynamic change. It was remarkable that standard errors were relatively smaller during these rapid changes than during the steady period in the middle of the game. These findings indicated that oxyHb decreased in the target region derived from playing the game, and that many children displayed common similar trends of rapid oxyHb changes.

In order to investigate the effects of maturity on hemodynamic responses, we determined correlation coefficients for children's ages, and mean values of oxyHb changes during the task period

Table 1
Individual data of oxyHb changes during the fighting game

Subjects	Age (year)	Gender	LA	RA	LP	RP
S1	14	M	–	D	–	D
S3	11	M	D	D	I	–
S5	12	F	D	D	–	D
S6	10	M	I	–	–	–
S7	11	M	D	D	D	D
S8	11	F	D	D	D	–
S9	10	M	D	D	D	D
S10	7	M	–	D	D	D
S11	13	M	D	D	–	–
S13	9	F	D	–	D	–

F, female; M, male; I, increase; D, decrease; –, not significant. The regions LA, RA, LP, and RP correspond to regions described in Fig. 2.

Table 2
Individual data of oxyHb changes and number of lines eliminated during the puzzle game

Subjects	Age (year)	Gender	LA	RA	LP	RP	Lines
S2	9	F	D	D	D	D	11
S3	11	M	D	D	–	I	36
S4	8	M	–	D	D	–	27
S5	12	F	I	I	I	I	30
S6	10	M	I	I	D	–	29
S8	11	F	–	–	–	–	6
S9	10	M	D	D	D	D	48
S12	9	M	D	D	D	D	43

F, female; M, male; I, increase; D, decrease; –, not significant. The regions LA, RA, LP, and RP correspond to regions described in Fig. 2.

in both game conditions ($n = 8$ and $n = 10$ for the puzzle game and the fighting game, respectively). As a result, no significant correlation ($P < 0.01$, uncorrected) was found in all regions for both games. Only one region, i.e., the right anterior region for the fighting game, indicated a negative correlation with $P = 0.046$ (uncorrected).

Effects of game performance on hemodynamic response were also analyzed. A number of lines eliminated in the puzzle game were used to evaluate game performance for each child, but the fighting game was not analyzed due to difficulties in scoring performance. Analysis also revealed no significant correlation ($P <$ 0.01, uncorrected) between mean values of oxyHb changes during the task period and game performance in any one region.

We compared mean values of oxyHb during the fighting game and the puzzle game, for the five children who played both games, using a paired t test to examine differences in hemodynamic response between both games. Consequently, no significant difference or trend was obtained between games although the magnitude of oxyHb decrease seemed to be greater in the fighting game than the puzzle game, as shown in Fig. 4.

Discussion

DPFC activity comparison between children and adults

The present paper suggests that the majority of children displayed a game-related oxyHb decrease in DPFC. A game-related decrease in oxyHb was also previously observed in adult subjects (Matsuda and Hiraki, 2004). A comparison between our present and previous studies suggests that children's patterns for the time series of oxyHb, which showed rapid changes after the beginning and end of the games, respectively, are very similar to those of adults, indicating relative similarities in the dynamic behavior of oxyHb during video game play between adults and children. Moreover, there was no significant correlation between children's age and oxyHb variations. These findings suggest that oxyHb decrease when playing a video game is a common phenomenon to adults and children at least older than 7 years old. However, it would be worthwhile to further examine trends of negative correlation between children's age and oxyHb variations which were observed in the right anterior region for the fighting game. This might reflect developmental changes of prefrontal function.

Subjects' total experience or skills of video games were variable, because we did not select subjects according to their experience in video games in both studies of adults and children. Performance for the puzzle game was actually variable as shown in Table 2. Nevertheless, a similar decrease in oxyHb was observed in many subjects and, a significant correlation between performance and oxyHb variations was not found. Thus, it is likely that subjects' experience in video games does not strongly affect oxyHb changes during video game play.

The majority of children showed a game-related oxyHb decrease, whereas a few children showed a game-related increase in some regions. It is difficult to interpret these minor results because no prominent tendency was found among the location of active regions, and children's age or performance. Although there are many possible factors such as individual variation of strategy for performing the games, and emotional state, further speculations require more evidence.

Origin of oxyHb decrease in DPFC

Why does oxyHb in DPFC, or rCBF in DPFC tend to decrease during video games? Since a video game consists of multiple stimuli such as colorful images and continuous sounds, it is unclear which constituent of the video game caused such hemodynamic changes in the present experiments. However, task-induced decreases of rCBF or BOLD in DPFC have been reported by previous studies using video-game-like tasks, e.g., a computer maze task (Ghatan et al., 1995), a driving game task (Calhoun et al., 2002; Walter et al., 2001), and a reaching task (Shimada et al., 2004). Each of these tasks and games employed in this study differs in various aspects such as purpose, manipulation, visual effects, and sounds. Nevertheless, task-related signal decreases in DPFC were commonly observed. Hence, it is reasonable to assume that oxyHb decrease in DPFC during video game play was not induced by specific aspects of each game, but rather by common aspects among many video-game-like tasks.

One possible factor applicable to such common aspects is the attention demand required for visual stimuli. Meta-analysis of 9 PET studies by Shulman et al. (1997b) has suggested that during 9

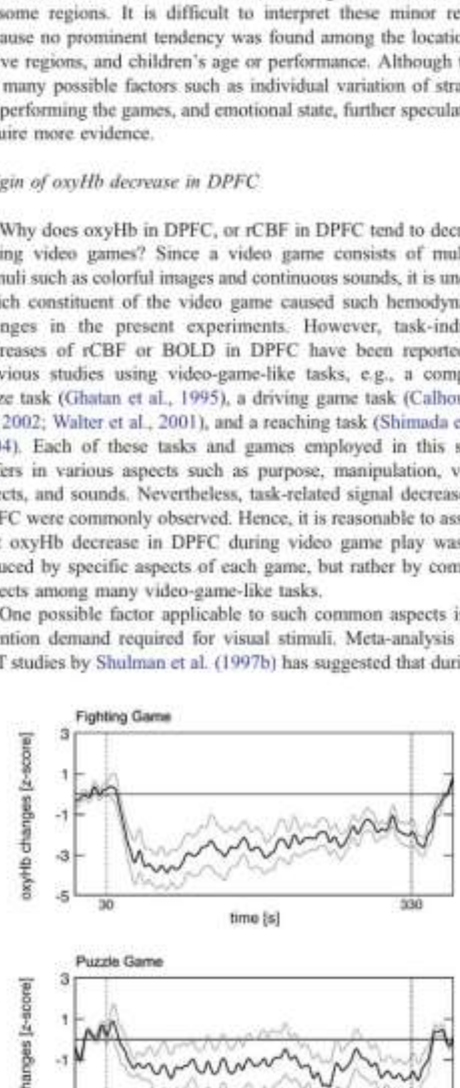

Fig. 4. The grand average for the time series of oxyHb concentration in the right anterior region. The bold line represents the mean change in oxyHb, while the thin line represents the standard error. The vertical bars at 30 s and 330 s represent the beginning and the end points of the game, respectively.

goal-directed tasks, rCBF decreases were consistently present in the medial frontal region running along a dorsal–ventral axis (BA 8, 9, 10, and 32). The goal-directed tasks which they analyzed, e.g., visual search, spatial attention, and language tasks had nothing in common except that all tasks required a response to certain visual stimuli. Thus, it is reasonable to think that the commonly observed rCBF decrease is related to attention to visual stimuli. Indeed, an fMRI study using a visual task (Mazoyer et al., 2002) demonstrated that there was a negative correlation between the load of sustained attention (or vigilance) toward visual stimuli, and the activity of the dorsal medial prefrontal cortex (DMPFC; BA 9, 10). In other words, the more subjects increased their attention to visual stimuli, the more the BOLD signal in DMPFC decreased.

This correlation probably corresponds to inhibition of DPFC activity. Even if an experimenter tells a subject not to think of anything while resting, total compliance is unlikely for the entire resting period. It is also probable that many kinds of mental activity occurred spontaneously in subjects during the resting period in our study. Shulman et al. (1997b) speculated that spontaneous thoughts such as those involved in monitoring the external environment or emotional states during passive conditions, requiring MPFC activity, may be suspended during active conditions in order to enhance task performances. Moreover, meta-analysis of 9 PET studies focusing on neural activity during resting states (Mazoyer et al., 2001) indicated common DMPFC activity in resting periods in each of the studies. Based on these and other findings on DMPFC activity, Gusnard and Raichle (2001) have suggested that DMPFC activity was due to cognitive processes concerning oneself, or that other mental states were attenuated when subjects needed to pay attention to external stimuli. A video game involves providing the player with goal-directed tasks, and most video games also require players to pay attention to a screen continuously. Accordingly, the oxyHb decrease in DPFC during video games probably has the same origin as reported by these findings.

Relations between video game play and attention demand have also been described in EEG studies. Some researchers have reported the occurrence of frontal midline theta rhythm (fm-theta) during computer game play (Laukka et al., 1995; Yamada, 1998; Slobounov et al., 2000). Fm-theta reflects attention concentration directed toward a task, and appears dominantly around Fz of the EEG 10-20 system. A recent study using simultaneous recording of EEG and fMRI indicated fm-theta-related negative BOLD signals in the frontal midline (BA 8) and superior frontal region (BA 9) (Mizuhara et al., 2004). These findings may also imply a correlation between visual attention and DPFC deactivation.

Task-induced decrease in rCBF or BOLD is not always related to neural inhibition. Origin of the signal decreases has never been fully explained, and there are other possible explanations apart from neural inhibition (Gusnard and Raichle, 2001; Wade, 2002). One possible explanation relates to passive hemodynamic changes called 'vascular steal' phenomenon. Decreases in signals are often observed around active areas. Their origin is sometimes interpreted as blood draining from neighboring areas to active areas and referred to as 'vascular steal'. However, in our case, we assumed that the game-related rCBF decrease in DPFC was not derived from the vascular steal for the following reasons. If decreases in rCBF observed in the present study were caused by the vascular steal, increases in rCBF should be observed in the neighborhood of our target area. Although we cannot refer to the outside of our target area directly, there were no active areas in DPFC during video-game-like tasks in previous studies as mentioned above (Ghatan et al., 1995; Calhoun et al., 2002; Walter et al., 2001). Moreover, Shulman et al. (1997a) reported that a common rCBF 'increase' was observed only in the visual cortex among the cerebral cortex, in their meta-analysis of 9 PET studies using visual tasks. Thus, it is reasonable to say that the common rCBF decrease in DPFC in their meta-analysis was not due to the vascular steal. Another possible explanation is temporary ischemia. It is possible that an area where neural activity actually increases cannot receive adequate oxygen for some reasons. In fMRI studies, BOLD signals sometimes decrease for a few seconds immediately after onset of a stimulus (Hu et al., 1997; Yacoub et al., 2001). This 'initial dip' phenomenon is interpreted as a temporary lack of oxygen caused by a rapid increase in neural activity. In this study, decreases in rCBF lasted for a few minutes, and it was unlikely that a lack of oxygen continued for such a long time in healthy subjects. Therefore, we can say that sustained decreases in rCBF demonstrated in this study did not arise from temporary ischemia related to increase in neural activity.

The relation between task-related decrease in rCBF and neural inhibition was also mentioned in some brain imaging studies on the outside of the prefrontal cortex such as the visual cortex (Shmuel et al., 2002; Smith et al., 2000), the motor cortex (Stefanovic et al., 2004; Allison et al., 2000), or the auditory cortex (Ghatan et al., 1998). These studies implied the existence of neural mechanisms whereby neural activity irrespective of a task was attenuated positively. Although results from studies on sensory areas cannot be directly applied to studies on the prefrontal cortex, it is likely that similar neural mechanisms are related to the game-related oxyHb decrease in DPFC in our study.

Technical problems of NIRS study on children

We had to exclude data from 7 children for analysis in this paper due to motion artifacts. Although NIRS is not as sensitive to motion artifacts as fMRI and PET, any quick motion shaking the optical fibers causes sharp changes in hemoglobin signals. Therefore, we instructed children to keep their heads still during measurements, but this was a problem for children without any stimulus during resting conditions. Some children also moved their head and body while playing video games in an absorbed manner. Improvements to the experimental design as well as the fiber holder are essential to solve these problems. For example, it could be effective to use a simple task, rather than rest as a control condition, and also to shorten measuring time for the trials.

A second limitation of this study was the general lack of understanding of experimental instructions. When we asked the children whether they understood our instructions, they always answered 'yes.' In reality, younger children tended to perform differently from stated instructions, and we had to re-record measurements or abandon collation of data. This problem may be solved by confirming comprehension of instructions by performing a practice trial identical to actual measurements. Elaborate revisions and modifications of the experimental techniques are inevitable in order not to waste valuable data obtained in future studies on the child brain.

Conclusions

Sustained oxyHb decrease in DPFC was observed during video game play in a majority of children, and time series patterns of oxyHb decrease in children were similar to those previously reported in adults. The oxyHb decrease in DPFC probably reflects neural inhibition, which is derived from attention demand for video games. Thus, we conclude that playing video games tends to attenuate DPFC activity compared to the resting state, and that this tendency is common to adults and children at least older than infants. This hemodynamic response probably arises from attention demand for video games rather than from subject's age and performance.

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ORIGINAL RESEARCH

Single event-related changes in cerebral oxygenated hemoglobin using word game in schizophrenia

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Ryo Fujiki[1,2]
Kiichiro Morita[1,2]
Mamoru Sato[1,2]
Yuji Yamashita[1,2]
Yusuke Kato[1,2]
Yohei Ishii[2]
Yoshihisa Shoji[1,2]
Naohisa Uchimura[1]

[1]Department of Neuropsychiatry, Kurume University, [2]Cognitive and Molecular Research Institute of Brain Diseases, Kurume University School of Medicine, Kurume-City, Japan

Abstract: Neuroimaging studies have been conducted using word generation tasks and have shown greater hypofrontality in patients with schizophrenia compared with healthy subjects. In this study, we compared the characteristics of oxygenated hemoglobin changes involved in both phonological and categorical verbal fluency between 35 outpatients with schizophrenia and 35 healthy subjects during a Japanese "shiritori" task using single-event-related near-infrared spectroscopy. During this task, the schizophrenic patients showed significantly smaller activation in the prefrontal cortex area than the controls. In addition, a significant positive correlation was obtained between oxygenated hemoglobin changes (prefrontal cortex area, inferior parietal area) and the severity of positive psychiatric symptoms. It is possible that hypofrontality of patients may be a diagnostic assistance tool for schizophrenia, and that the relationship between activation and positive syndrome scores may be of help in predicting functional outcome in patients.

Keywords: word production task, single-event-related near-infrared spectroscopy, schizophrenia, hypofrontality, biological marker

Introduction

A number of neuroimaging studies have been conducted using word generation tasks and have reported greater frontal hypoactivity in patients with schizophrenia compared with healthy subjects.[1–3] Shiritori is a very popular word game in Japan and it is possible to play from 3 years old or more.[4] This game requires players to generate a noun that begins with the last character of the noun given by the preceding player, necessitating players to retain information about characters and manipulate information – that is, working memory.

Near-infrared spectroscopy (NIRS), which estimates brain activity by measuring relative changes in oxygenated hemoglobin (oxy-Hb) concentration at the surface of the brain, has increasingly been performed for several neuropsychological tests of brain functions. Advantages of this apparatus are the lack of sensitivity to body movement; it's relatively small size, portability, and inexpensiveness as compared to other neuroimaging settings;[1,2] and it enables the researcher to create a mapping of the brain's functional activities; thus, this machine is possibly a useful tool for assessing cortical activation patterns of patients with schizophrenia during shiritori performance. To our knowledge, previous findings have not been reported regarding the cortical activation between patients with schizophrenia and healthy subjects during a shiritori task using NIRS; however, there have been functional magnetic resonance imaging (MRI) and magnetoencephalography studies using this task in only healthy subjects.[4,5]

Correspondence: Ryo Fujiki
Department of Neuropsychiatry and Cognitive and Molecular Research Institute of Brain Diseases, Kurume University School of Medicine 67, Asahi-Machi, Kurume-City, Japan
Tel +81 942 31 7564
Fax +81 942 35 6041
Email fujiki_ryou@med.kurume-u.ac.jp

The present study investigated single-event-related changes in cortical activation during a shiritori task in healthy subjects and patients with schizophrenia by using a multichannel NIRS machine.

The purposes of this study were to investigate different activity patterns in patients with schizophrenia compared with those in healthy subjects and to find the relationship between psychiatric symptoms and functional brain activities. We assumed that relative frontal hypoactivation would be found in schizophrenic patients compared to healthy subjects and that an association between activation and symptom scores could be an indicator of clinical outcome, as in previous studies.

Materials and methods

Participants

This study enrolled 35 outpatients with schizophrenia (19 males and 16 females; mean age, 29.4±5.8 years, paranoid type) and the same number of healthy control subjects (19 males and 16 females; mean age, 27.6±6.8 years). In accordance with the International Classification of Disease, tenth revision, two attending psychiatrists diagnosed patients.[6] All participants were native Japanese speakers and were judged from the Edinburgh Inventory to be right-handed.[7] The Japanese version of the National Adult Reading Test assessed their mean intelligence quotient (IQ) values.[8] No subjects had a head injury, neurologic disorder, alcohol/substance abuse, epilepsy, visual disabilities, aphasia, or dyslexia. The healthy subjects had no history of psychiatric disorders or familial history of psychosis. The schizophrenic patients were taking atypical antipsychotic medications (ie, risperidone [n=19], olanzapine [n=12], and quetiapine [n=4]) and were assessed by the Positive and Negative Syndrome Scale (PANSS).[9] All of them were engaged in a community workshop and/or housework. The mean daily antipsychotic dose in terms of haloperidol equivalent was 7.5±1.8 mg.[10] Adequate informed consent was obtained from all subjects. This study was approved by the ethics committee of Kurume University. Demographic and clinical characteristics of all subjects are shown in Table 1.

Table 1 Subject characteristics

	Patients	Controls	*P*-value
Age (year)	29.4±5.8	27.6±6.8	0.25
Sex (F/M)	19/16	19/16	
Education (year)	13.9±1.3	15.7±1.6	<0.05
IQ	100.3±8.1	103.2±5.3	0.08
Illness duration (year)	4.2±1.9		
PANSS score			
Positive subscale	18.2±4.9		
Negative subscale	19.9±3.6		
General score	41.0±4.3		
Medication			
HPD equivalent (mg/day)	7.5±1.8		

Note: Values are expressed as mean ± standard deviation.
Abbreviations: F, female; HPD, haloperidol; IQ, intelligence quotient; M, male; PANSS, Positive and Negative Syndrome Scale.

Procedure

NIRS measurement

A 44-channel NIRS system (ETG4000; Hitachi, Tokyo, Japan) measured oxy-Hb changes during tasks covering from the frontal to temporoparietal regions. Oxy-Hb changes were calculated from the difference in absorbance based on the modified Beer–Lambert law. The middle point of the injector–detector probe pairs was defined as a channel. The depth of each channel is supposed to measure changes at points 2 to 3 cm from the scalp that correspond to the cerebral cortical surface.[11,12] According to the International 10–20 system used in electroencephalography, we placed probes along the Fp1–Fp2 line to the lowest anterior probes; left channel 19 and right channel 22 (Figure 1A). To avoid movement artifacts, participants were instructed to minimize their movements and jaw fixation during examination. The pre-task baseline was determined as the mean during 1 second preceding the word presented, while the post-task baseline was determined as the mean during 1 second from 10 to 11 seconds after the word was presented. Linear fitting was applied to the data between these two baselines. For the relationship between each channel and anatomic region, NIRS data were converted to a normalized brain image template (three-dimensional composition indication unit; Hitachi).

Task design

Brain activation was measured during word production. The advantage of NIRS is that it is relatively insensitive to body movements during measurement; therefore, this apparatus can obtain data in an overt task. For this examination, each subject sat on a comfortable chair and was required to perform word production. One session consisted of two contrasting conditions (word production task, control condition), and all subjects alternated between these conditions. Each word was visually presented by a monitor for 0.3 seconds as an activation task and a fixed circle was presented for 12 seconds. In the activation task, subjects had to immediately generate a noun that starts with the last kana character of the presented word and they were required to say only animal nouns. Thus, this task was the animal category version of the Japanese shiritori word game, as well as a word production task. For example,

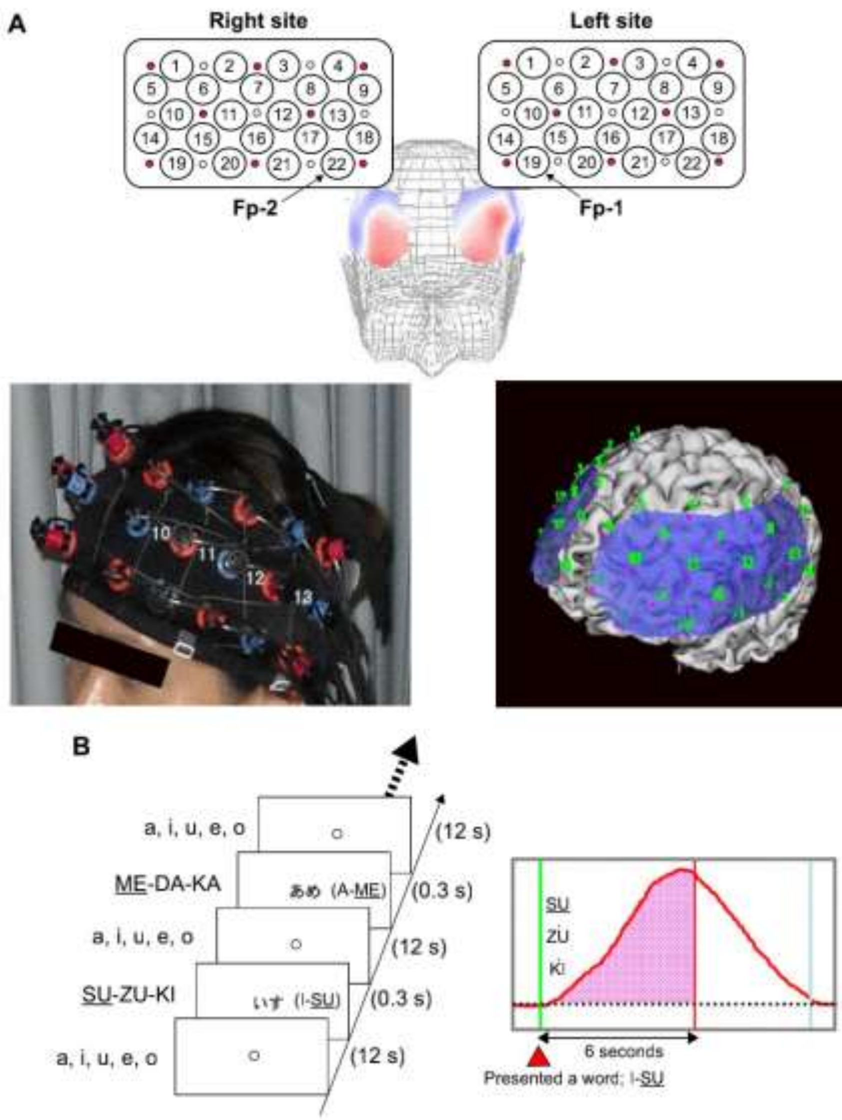

Figure 1 Study design: (**A**) location of channels, (**B**) protocol.
Notes: (**A**) Subjects were instructed to generate a noun for a presented word. This procedure was repeated 20–25 times. Subjects had to generate a noun-only creature. This task is the creature category and letter version of the verbal shiritori task. (**B**) Data were calculated from the mean wave of oxy-HB changes. The area of the waveform of oxy-HB changes 6 seconds after the presented word was calculated and we used values of this area as NIRS data.
Abbreviations: NIRS, near-infrared spectroscopy; oxy-HB, oxygenated hemoglobin; s, seconds.

when the noun "I-SU" (chair) was presented, the subject said the noun "SU-ZU-KI" (sea bass). In the control condition, subjects were required to say the syllables "A-I-U-E-O" repeatedly. The word production task was repeated 20–25 times per session. Waveforms of 20 correct responses for each subject were adopted as law data, and we discarded waveforms of incorrect responses and responses over 1 second after the presented task. Averaged waveforms for the 20 correct responses were analyzed using the "integral mode" of the apparatus. Oxy-Hb changes between activation and control periods were expressed numerically for every 100 milliseconds. NIRS data were calculated from the mean wave of oxy-Hb changes.

The area of the waveform 6 seconds after the presented word was calculated because peak latency of healthy subjects was 5.0±0.9 seconds during this task in a pilot study, and we used values of this area as NIRS data (Figure 1B).

Statistical analysis

Raw NIRS data were preprocessed by applying a low pass filter with cutoff frequencies of 0.5 Hz. We used histograms at each channel to confirm a normal distribution. Performance and oxy-Hb changes at each channel in controls were compared with those of patients with schizophrenia using an unpaired t-test. For analyzing cortical activation, we adopted the false discovery rate correction method (Benjamini and Hockberg method)[13] and set the value specifying the maximum false discovery rate to 0.05. Next, to evaluate the relationship between activation and the PANSS score/profile, the Pearson's product–moment correlation coefficient was calculated. For $-0.4<r<0.4$, it is considered to be a low correlation (not very significant); correlation coefficients were accepted as significant at $r>0.4$ and $r<-0.4$. $P<0.05$. The averaged values were expressed as mean ± standard deviation. Strangman et al reported that oxy-Hb changes correlate more strongly with blood-oxygen-level dependent (BOLD) functional MRI signal than do deoxygenated hemoglobin changes; therefore, we adopted the oxy-Hb changes as activation data.[14]

Results

Performance of word production task

Word production was 21.1±1.8 words in the schizophrenic patients and 21.5±0.9 words in the healthy controls. There was no significant difference between the groups (unpaired t-test: t=1.6, P=0.120).

Activation during word production task at each channel

The healthy subjects had significantly larger activation than the patients with schizophrenia at five channels (left channel 2, unpaired t-test: t=3.0, degrees of freedom [df]=68, q=0.004; left channel 11, unpaired t-test: t=3.5, df=68, q=0.001; left channel 12, unpaired t-test: t=3.0, df=68, q=0.003; left channel 19, unpaired t-test: t=3.6, df=68, q<0.001; and right channel 17, unpaired t-test: t=3.1, df=68, q=0.003; q-value =0.001–0.006) (Figure 2). Waveforms are shown in Figure 3.

Correlation between oxy-Hb changes and PANSS scores or performance

Oxy-Hb changes at left channel four, left channel seven, left channel ten, left channel eleven, right channel one, right channel eight, and right channel 13 revealed a significant positive correlation with positive symptom scores in patients (r=0.45, P=0.003; r=0.41, P=0.007; r=0.48, P=0.002; r=0.51, P=0.001; r=0.44, P=0.006; r=0.41, P=0.008; and r=0.44, P=0.005, respectively); however, there was no correlation with negative symptom scores (Figure 4). No correlation was found between performance and activation in both groups. In the schizophrenic patients, oxy-Hb changes at each channel showed no significant correlation with illness duration and antipsychotic drug dose. We investigated the relationship between activation and each drug, and did not find any statistical significance. There was no significant correlation

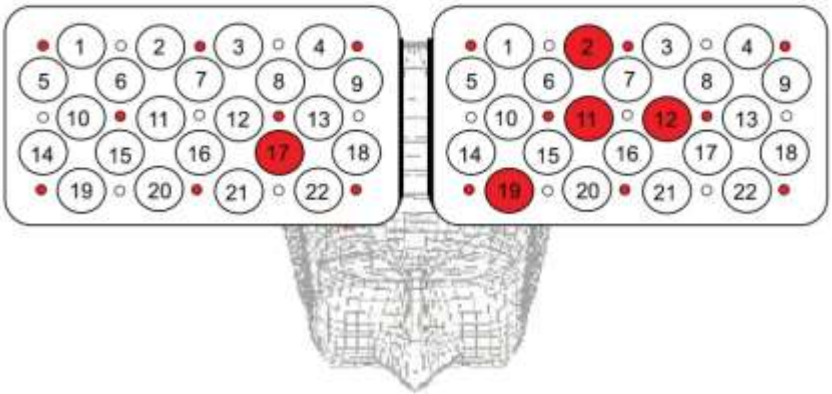

Figure 2 Maps of cortical distribution of channels that were significantly smaller in patients than in healthy subjects.
Note: Statistically significant channels are colored red.

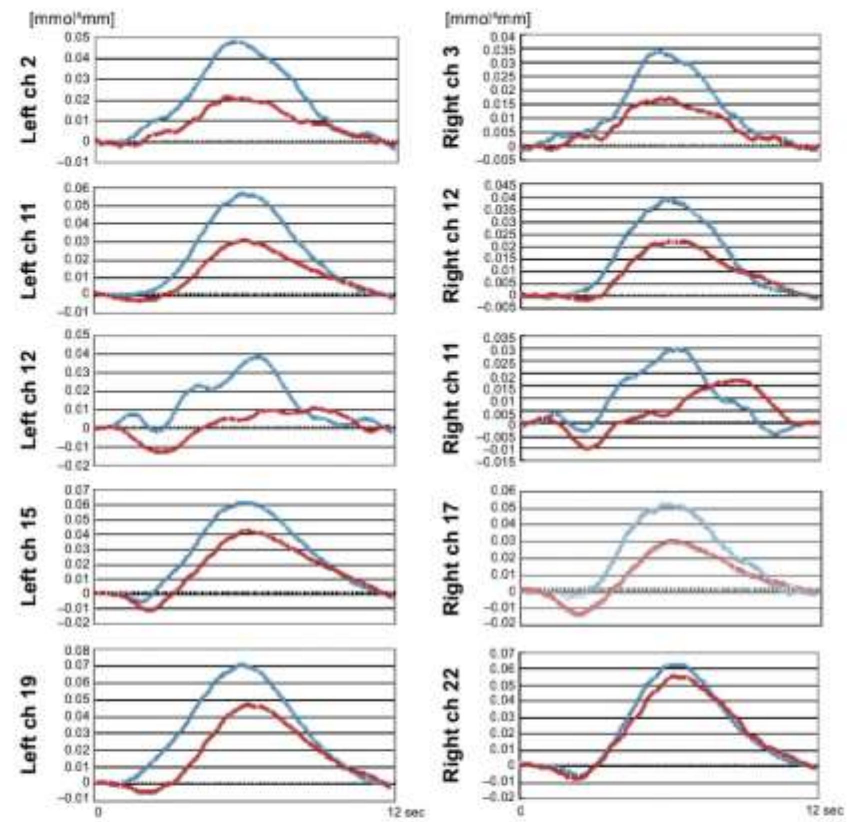

Figure 3 Waveforms in healthy subjects and patients at significantly different activation channels.
Note: Blue lines are healthy subjects and red lines are patients.
Abbreviation: ch, channel.

between performance and PANSS scores or IQ. In addition, there was no significant correlation between medication and PANSS scores or IQ.

Discussion

We compared hemodynamic changes between patients with schizophrenia and healthy subjects during a word production task using a single-event-related NIRS. In addition, we investigated the relationship between regional activation and PANSS scores in patients. A previous study suggested that NIRS measurement using an event-related method enables researchers to obtain more efficient averaging and to be free from artifacts.[15] Thus, we thought that this task of performing overt word production would enable the evaluation of psychiatric patients. This task is associated with the characteristics of both letter and categorical verbal fluency and requires several cognitive functions, such as retrieval, attention, and working memory. In Japanese, Sumiyoshi et al showed no difference in degree of impairments between the letter and category version of this task.[16] The present study showed pronounced hypoactivation of the prefrontal cortex (PFC) area in the schizophrenic patients compared to the healthy subjects as in other studies,[1,2,17–20] while it has been reported that hyperactivation is a feature of the schizophrenic patients.[21] Manoach suggested that both findings reflected PFC dysfunction in schizophrenia, rather than that one of them explained the characteristics of inefficiency in patients.[21] Van Snellenberg et al reported that the relationship between an increase in load on working memory and PFC activation showed an inversed U-curve:[22] PFC activation was enhanced as the load increased, but then declined after exceeding a specific level even in healthy subjects.[20,22] In patients with schizophrenia, this curve may shift leftward and reach a peak in the presence of a small load. The presence

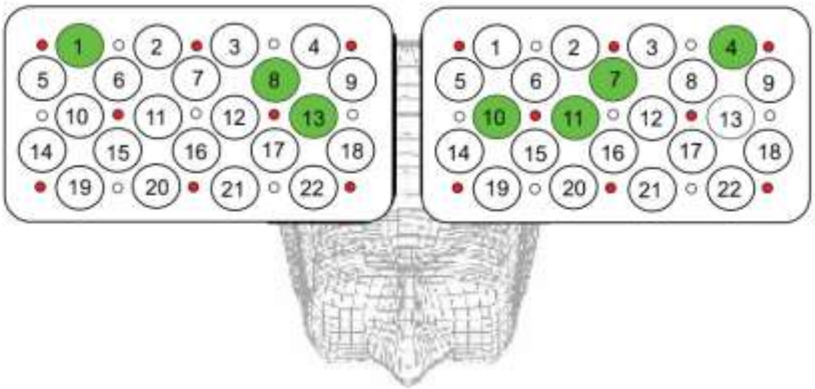

Figure 4 Cortical distribution of significant correlations between activation and PANSS scores.
Note: Statistically significant channels correlated with positive symptom scores are colored green.
Abbreviation: PANSS, Positive and Negative Syndrome Scale.

of hypofrontality in schizophrenic patients was likely to be associated with the difference in the difficulty level between the groups even when performing the same task. According to the waveforms presented at each channel, it seemed that the difference between the groups showed in the amplitude rather than the latency of waveform, although we could not test this exactly. We thought that the hypofrontality of the schizophrenic patients was influenced by a lesser degree of activation rather than a more delayed activation. Further study is needed to examine these points in detail.

In short, it is suggested that a heavy load was imposed on the schizophrenia patients compared to the healthy subjects, although task performance showed no significant differences between groups. However, there are some issues regarding hyperfrontality/hypofrontality that have to be mentioned. Schizophrenia has been associated with deficits in attention, executive processes, and working memory;[23] therefore, the reduced activity of the schizophrenic patients might have been due to decreased motivation, fatigue, or impaired attention specific to the disease. Taking these issues into account, we ensured that the number of task executions for one session was less than the event-related potential of electroencephalography, and the total time of an examination for each subject was less than 5 minutes.

We investigated the relationship between functional brain activity and PANSS scores. Previous studies have demonstrated a significant correlation between PFC activation and psychiatric symptoms.[18,24–26] In the present study, there was a correlation not only with the PFC area (left channel 7, 10, 11; right channel 8, 13) but also with the inferior parietal area (left channel 4, right channel 1). In working memory tasks such as the verbal fluency test, past studies have showed that the phonological loop is associated with the left inferiorparietal region and that the central executive system is associated with the prefrontal region.[27] Thus, we suggest that these findings reflect the fact that PFC function was involved in the word production task and inferior parietal function was induced by phonological working memory. It is possible that the relationship between right inferiorparietal activation and PANSS positive subscale reflect inefficiency of schizophrenia; this finding may be the result of a compensation mechanism.

Our results suggest that cortical activation predicts the outcome of patients, as suggested by previous findings.[18,24–26] Therefore, it is believed that hypofrontality of schizophrenic patients may be a trait marker, a view that is controversial, and the relationship between activation and PANSS scores may be a state marker in patients with schizophrenia. A previous study attempted to identify the specific psychiatric disease during the verbal fluency task using NIRS, but failed to prove that the method was a useful diagnostic tool.[17] Indeed, hypoactivation of several psychiatric disorders, such as mood disorder, dementia, anxiety disorder, and eating disorder have been reported.[28–35] Our findings on hypoactivation are limited to biological markers in a psychiatric disease, so further studies are needed to find disease-specific features.

There are some limitations to the present study. First, the spatial resolution of NIRS is lower than that of MRI. We converted our data to a normalized brain image template for the relationship between recording site and anatomic region

(Figure 1A). In addition, we adopted the International 10–20 system for brain mapping as in a previous report.[36] Second, regarding such artifacts as body movement and muscle activity, NIRS is relatively insensitive to body movement and can be performed in a natural posture, but artifacts are likely to be produced by nodding and rotation of the head. We therefore employed jaw fixation and data averaging using the event-related method, which is insensitive to noise because of low-frequency signal components, to reduce artifacts as much as possible.[15] A previous study also investigated the relationship between frontotemporal muscle activity and NIRS signal,[37] and found no significant correlations. Third, regarding medications, all patients received atypical antipsychotic drugs, with which cognitive impairment has been associated.[38,39] However, cognitive impairment has been reported in untreated patients with schizophrenia, in patients about to begin treatment, and in patients at the clinical onset of schizophrenia, as well as in healthy first-degree relatives of patients with schizophrenia.[40–43] In this study, there was no relationship between activation and each drug; however, future studies should investigate drug-naive patients. Fourth, regarding task performance, there were no differences in performance between groups. The present study investigated only waveforms of correct responses and only adopted data of responses of less than 1 second, but we did not measure reaction time. Fifth, although this study did not investigate the difference between oxy-Hb and deoxygenated hemoglobin, we adopted oxy-Hb changes as data similar to previous study[14] because BOLD signal and NIRS signal has been investigated in the different types of blood vessels. Therefore, further studies are needed to examine this point in detail.

In summary, this study performed a single-event-related NIRS method during a shiritori game task involving characteristics of both letter and category verbal fluency in patients with schizophrenia versus healthy controls. We revealed reduced PFC activity and a significantly positive correlation between oxy-Hb changes and positive psychiatric symptom scores in patients with schizophrenia. It is possible that hypofrontality of patients is not a disease-related feature, and may be a diagnostic assistance tool for schizophrenia. In addition, an observed relationship between activation and PANSS scores may be of help in predicting functional outcome in patients.

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Disclosure

The authors report no conflicts of interest in this work.

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RESEARCH ARTICLE

Neuronal Correlates of Cognitive Control during Gaming Revealed by Near-Infrared Spectroscopy

Matthias Witte[1,2]*, **Manuel Ninaus**[1], **Silvia Erika Kober**[1], **Christa Neuper**[1,2,3], **Guilherme Wood**[1,2]

1 Department of Psychology, University of Graz, Universitaetsplatz 2, 8010 Graz, Austria, **2** BioTechMed Graz, Graz, Austria, **3** Laboratory of Brain-Computer Interfaces, Institute for Knowledge Discovery, Graz University of Technology, Inffeldgasse 12/IV, 8010 Graz, Austria

* matthias.witte@uni-graz.at

Abstract

In everyday life we quickly build and maintain associations between stimuli and behavioral responses. This is governed by rules of varying complexity and past studies have identified an underlying fronto-parietal network involved in cognitive control processes. However, there is only limited knowledge about the neuronal activations during more natural settings like game playing. We thus assessed whether near-infrared spectroscopy recordings can reflect different demands on cognitive control during a simple game playing task. Sixteen healthy participants had to catch falling objects by pressing computer keys. These objects either fell randomly (RANDOM task), according to a known stimulus-response mapping applied by players (APPLY task) or according to a stimulus-response mapping that had to be learned (LEARN task). We found an increased change of oxygenated and deoxygenated hemoglobin during LEARN covering broad areas over right frontal, central and parietal cortex. Opposed to this, hemoglobin changes were less pronounced for RANDOM and APPLY. Along with the findings that fewer objects were caught during LEARN but stimulus-response mappings were successfully identified, we attribute the higher activations to an increased cognitive load when extracting an unknown mapping. This study therefore demonstrates a neuronal marker of cognitive control during gaming revealed by near-infrared spectroscopy recordings.

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Introduction

Goal-oriented behavior requires an orchestrated network of brain activations including sensory, motor and cognitive processes [1,2]. These processes have been summarized under the term 'cognitive control'. For an effective control, our brain frequently has to link a given stimulus to an appropriate behavioral response. Stimulus-response mappings of this kind are therefore a central component of inductive reasoning [3] allowing for quick and adaptable human behavior.

Competing Interests: The authors have declared that no competing interests exist.

There is an extensive literature on stimulus-response mappings that assessed how associations are formed and maintained [4]. This past research can be summarized under the term rule-guided behavior and has mostly relied on experiments using single responses to a given cue, for example in the Wisconsin Card Sorting Test [5] or in the Brixton Spatial Anticipation Test [6]. The neuronal populations involved in rule-guided behavior have been located in a distributed network across frontal, parietal and temporal brain regions [4,7,8]. Prefrontal cortex plays an important role [9] and especially the left dorsolateral prefrontal cortex (dlPFC) has been linked to the maintenance of rules [4,10]. Recent studies further suggested a specific regional organization. In particular, more complex rules involve progressively more anterior regions [7,11]. Yet, there is also growing evidence for a role of dlPFC in early phases of rule extraction and learning [12–14]. It thus seems that activations across brain areas may change along with the acquisition of a new rule. This idea was recently support by findings using a spatial rule attainment task [13] that demonstrated early dlPFC and frontopolar activations shifting to temporal and premotor regions when the rule was established. More general, a fronto-parietal control network has been linked to an initial adaptive mode of control [15,16].

Despite these insights coming from fMRI, only a few researchers applied event-related designs using electroencephalography. Mostly a late positive component has been described [17–20] reflecting either rule violation or hypothesis evaluation and generalization. Li et al. [21] showed that this positivity decreased from learning to application periods suggesting similar dynamics as revealed by the fMRI results mentioned above. However, the majority of experiments were based on artificial language grammar or arithmetical tasks. There is a lack of studies on naturalistic settings that monitor brain activations during continuous tasks. One exception is a recent study showing changes in theta power of electroencephalography after video game playing that resulted in enhanced performance in cognitive control tasks [22].

In the current approach, we therefore explored neuronal activity during game playing that involved simple stimulus-response mappings. We used a previous 2D game of ours [23] where participants had to catch falling objects. Those objects either fell randomly (RANDOM task), according to a known stimulus-response mapping based on color or shape (APPLY task), or according to an unknown mapping of the same type (LEARN task). We expected performance increases from RANDOM to LEARN to APPLY reflecting the different levels of task complexity (see Material and Methods for details). In addition, once a stimulus-response mapping is known and validated participants should perform better at catching the next objects falling. Near-infrared spectroscopy (NIRS) allowed exploring neuronal activity related to processes of cognitive control during gaming. NIRS is similar to fMRI in that it reflects the hemodynamic response in cerebral vessels [24–26]. The observed changes in hemoglobin concentration have been recorded in different movement paradigms [27,28] and can even represent activations during motor imagery [29,30]. Compared to most fMRI scanning protocols, NIRS offers a better time resolution [31,32] and is more mobile and robust to movement artifacts [33]. Prior studies have shown specific hemoglobin changes in prefrontal cortices during tasks of working memory [34–37] and video game playing [38,39]. We thus hypothesized that modulating the demands of cognitive control in a game task should be detectable in non-invasive NIRS signals over a network of different brain regions.

Material and Methods

Participants

Sixteen healthy adults (9 female, 7 male, mean age = 23 ± 2 years) enrolled in the current study after giving written informed consent. All of them were right handed, had no history of neurological or psychiatric disorders and had normal or corrected-to-normal vision. One additional participant was excluded from the analysis due to an increased amount of artifacts in the recorded brain activations. The study was approved by the local ethics committee (University of Graz) and is in accordance with the ethical standards of the Declaration of Helsinki.

Gaming task

We designed a simple 2-D game 'U get it U catch it' (Fig 1A; online information at http://studies.seriousgamessociety.org) in Matlab (The MathWorks, Natick, USA), where participants had to catch falling objects with a moveable paddle by pressing three predefined keys (arrow left, middle, right) of a conventional computer keyboard. Objects fell, one after each other including a 500 ms pause between objects, from top to bottom in 20 steps with a high speed of 50 ms/step. This fast pace was chosen based on pilot data to ensure that objects could only be caught with knowledge of the stimulus-response mappings described below. The path was created by interpolating a route of six basic steps composed of left, middle and right positions. For the last three steps the object did not change position to enable appropriate responses of the player. Objects differed in shape (circle, rectangle or triangle) and color (red, green or black).

To assess stimulus-response mappings of inductive reasoning, we implemented three experimental tasks. Each task was composed of 12 falling objects within a block and these sequences were repeated over 12 randomized blocks interleaving all experimental tasks (n = 36 blocks across tasks). Hence, participants had to switch between the different tasks so that motivation and attention could be kept high. During the RANDOM task objects fell randomly into the three slots. During the LEARN task objects fell according to an unknown but learnable regularity defined either by color or shape. These regularities were fixed one-to-one mappings, e.g. red

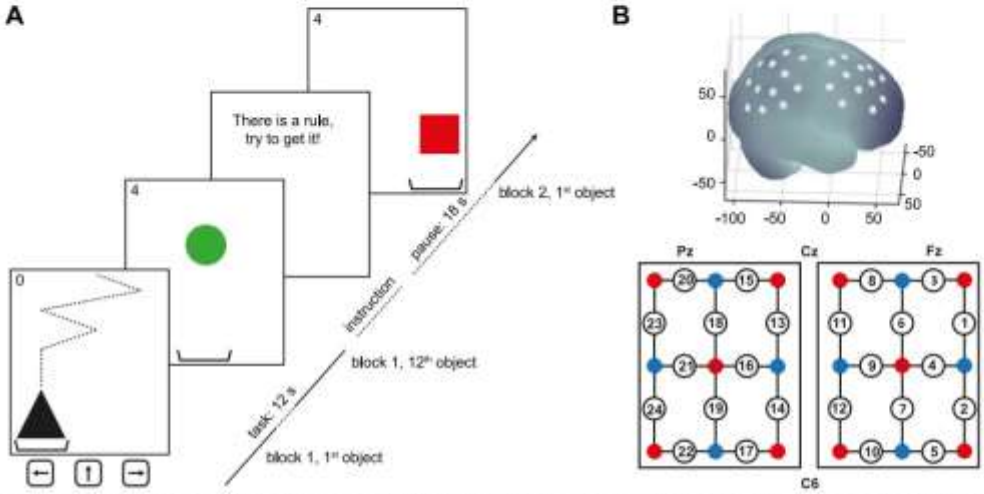

Fig 1. Experimental setup. (A) The 2D game displayed objects differing in color and shape on a computer screen. After an instruction, objects had to be caught by pressing the arrow keys associated with one of the three possible slots. A high-score in the upper left corner indicated the current performance. (B) Projections of the 24 channel positions (white points) on a MNI-152 compatible canonical brain. Two connected optode probe sets were positioned over the right hemisphe Similar to Fig 2 of the manuscript, these curves represent the amount of hemoglobin difference oxy-deoxy (delta Hb) in relation to the cumulative sum of objects successfully caught. This time each plot illustrates the grand average for our predefined ROIs (prefrontal: channels 1–5; sensorimotor: channels 11–14; parietal: channels 20–24). The rationale was to verify that the higher reactivity during the LEARN task can be found in each of these regions, as can be clearly corroborated here. In addition, one can observe an intermediate increase for activations of sensorimotor areas during the RANDOM task possibly reflecting the correlate of motor responses per se. Cost-benefit curves for the different ROIs re according to the international 10/20 placement system. Red and blue circles indicate sensors and detectors, respectively. Numbers refer to the recorded NIRS channels.

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objects will fall to the left slot, green to the middle and black to the right. They were tested in pilot experiments and became fully evident after three objects at earliest. After completion of each of these blocks, participants had to fill out a multiple-choice questionnaire asking for the presumed stimulus-response mapping. Finally, the APPLY task followed the same type of mappings but this time the regularity was explicitly stated before the beginning of the block (and thus not questioned afterwards). For example, the message on screen would read 'Color defines the rule: red objects fall to the left, green objects to the middle and black objects to the right'. Similar messages were displayed for the other tasks: 'There is no rule' for RANDOM and 'There is a rule: try to get it!' for LEARN.

An experimental session started with three test blocks to ensure that all tasks were understood. Then, participants played the whole set of randomized 36 blocks with self-paced initiation of the next block within the sequence by button press (delay to start 18 s). The behavioral performance was statistically analyzed in a 3 x 3 x 3 repeated measures ANOVA including within-subject factors TASK (random vs. learn vs. apply), BLOCK (block 1 to 4 vs. block 5 to 8 vs. block 9 to12) and OBJECT (object 1 to 4 vs. object 5 to 8 vs. object 9 to12). Assessing performance changes over objects within a block allowed us to monitor specific effects of the different tasks at hand. In addition, changes over blocks can reveal general effects over the whole task period, i.e. whether participants improve due to repetition or suffer from fatigue. Post-hoc t-tests were applied (Bonferroni correction) and all statistics considered a type I error of 0.05.

NIRS recording and analyses

We assessed changes of hemoglobin using a continuous wave system (ETG-4000, Hitachi Medical Co., Japan; for details see [30]). To this end, two 3 x 3 optode probe sets (24 channels, 3 cm inter-optode distance) were mounted over right cortices, aligned to the central point Cz of to the international 10/20 placement system (Fig 1B). The rationale for this setup was that we wanted to reduce influences of the right moving hand and instead targeted neuronal correlates of the cognitive processes during gaming. The three-dimensional coordinates of the NIRS channels were mapped onto MNI space using ELPOS (zebris Medical GmbH) and brain areas were identified based on the 1988 Talairach Atlas (Table 1; for details see [30]). NIRS signals were sampled at 10 Hz and stored on a conventional computer.

For offline analyses, we explored relative concentration changes (in m(mol/l) x mm) of oxygenated (oxy-Hb) and deoxygenated hemoglobin (deoxy-Hb) using custom-written Matlab routines. Raw signals were semi-automatically cleared from artifacts (criterion: amplitude of Hb-signal $>+/-$ 3 SD) and filtered in a range 0.01 to 0.9 Hz (zero phase-lag Butterworth). Next, task-related activations were obtained by referring time courses during gaming (0 to 12 s) to a pre-task baseline interval (-5 to 0 s).

NIRS activations in motor tasks have revealed a distinct increase of oxy-Hb and concurrent decrease of deoxy-Hb [27,40]. Moreover, the difference between oxy-and deoxy-Hb is an adequate marker of cerebral blood flow [41,42]. We therefore quantified this difference for each channel and defined three regions of interest (ROI): a prefrontal region (channels 1 to 5), a central region (channels 11 to 14) and a posterior parietal region (channels 20 to 24). The rationale was that these ROIs have a prominent role in associative response behavior [4,13] while the selected channel locations in our setup are still distant enough to avoid potential activation overlap.

Differences between the experimental tasks in these ROIs were statistically analyzed in a 3 x 3 repeated measures ANOVA including within-subject factors TASK (random vs. learn vs. apply) and ROI (prefrontal vs. central vs. parietal). Difference-Hb was assessed as mean activations in the time window 6 to 12 s because of the commonly observed time-lag in movement-related NIRS studies [27].

Table 1. Anatomic labeling.

Channel	Brodmann area	Description
1,4,7	8,9	Includes FEF, DLPFC
2	9,10	DLPFC, FPA
3,6,9	6,8	PMC and SMA, includes FEF
5	10,46	FPA, DLPFC
8,11	6	PMC and SMA
10	6,8,9	PMC and SMA, includes FEF, DLPFC
12	4,6	MI, PMC and SMA
13	3,4,6	SI,MI, PMC and SMA
14	1,2,40	SI, supramarginal gyrus (Wernicke's area)
15,18	5,7	Somatosensory association cortex
16	2,5,40	SI, somatosensory assocation cortex, supramarginal gyrus (Wernicke's area)
17	40	Supramarginal gyrus (Wernicke's area)
19,22	39,40	Angular gyrus, supramarginal gyrus (Wernicke's area)
20	7	Somatosensory association cortex
21	7,19,39	Somatosensory association cortex, V3, angular gyrus (Wernicke's area)
23	7,19	Somatosensory association cortex, V3
24	19	V3

Abbreviations: DLPFC dorsolateral prefrontal cortex; FEF frontal eye field; FPA frontopolar area; MI primary motor cortex; PMC premotor cortex; SMA supplementary motor area; SI primary sensory cortex; V3 tertiary visual cortex

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To compare the neuronal activations across tasks, similarity analyses have been suggested [43,44]. These techniques are helpful to transform multivariate patterns into similarity matrices that allow inference of the relationships among the data. We applied multidimensional scaling that has been often used in cognitive psychology for data visualization [45,46]. In particular, we used the smacof (scaling by majorizing a complicated function) algorithm [47] with maximal $n = 1000$ iterations and a random start configuration. The input data were defined as the pairwise correlations between all channels in a time window 6 to 12 seconds. The resulting two-dimensional space represents the distances between the input channels in a way to best approximate their given dissimilarities, i.e. one minus the correlation coefficients.

Results

Behavioral performance

We first assessed the percentage of objects successfully caught by each participant to evaluate the gaming performance. In general, the game was hard to play so that participants succeeded in 35% on average. Statistical testing of the dependent variable 'objects caught' in an ANOVA revealed significant main effects for all within-subject factors TASK ($F(1,15) = 9.31$, $p < 0.001$, $\eta 2 = 0.40$), BLOCK ($F(1,15) = 6.90$, $p < 0.01$, $\eta 2 = 0.33$) and OBJECT ($F(1,15) = 21.50$, $p <$ 1e-5, $\eta 2 = 0.61$). Participants caught more objects during the APPLY task ($M = 40$, $SE = 7\%$) when compared to LEARN ($M = 32$, $SE = 6\%$) or RANDOM ($M = 33$, $SE = 2\%$) indicating that pre-known regularities improved the performance. They also were more successful in the middle ($M = 36$, $SE = 3\%$) and last block ($M = 36$, $SE = 5\%$) than in the first block ($M = 33$, $SE = 3\%$) and caught more of the last four objects ($M = 40$, $SE = 6\%$) when compared to the first

($M = 32$, $SE = 4\%$) and middle part ($M = 33$, $SE = 4\%$) of falling objects. These overall results could suggest an improvement both due to task-specific effects within blocks and due to general repetition effects over longer periods across blocks. The significant interaction TASK x BLOCK ($F(1,15) = 3.29$, $p < 0.05$, $\eta 2 = 0.19$) and an interaction TASK x OBJECT ($F(1,15) = 16.47$, $p <$ 1e-5, $\eta 2 = 0.54$) allowed to further clarify the different improvements. Post-hoc tests (see S1 Table) indicated that only for the APPLY task more objects were caught in the last block compared to the first block. In addition, the last objects within a block were caught more often than the middle part. Both of these improvements point towards familiarization effects that will be discussed below. Most importantly, participants caught more of the last objects within a block when compared to the first and middle part of falling objects during LEARN suggesting that the stimulus-response mappings were correctly identified in the course of a given block. As expected, no significant differences were revealed for the RANDOM task: due to random stimulus-response mappings and the fast pace of falling objects, participants were not able to improve their performance.

The multiple-choice questionnaires filled out after each LEARN block indicated that across participants 88 ± 8% of the regularities were correctly identified. There was no effect of the type of mapping, i.e. color was as informative as shape ($t(15) = -1.18$, $p = 0.26$).

Brain activations revealed by NIRS

The most consistent pattern of changes in NIRS signal across participants and channels was an increase in relative oxy-Hb concentration along with a decreased deoxy-Hb level (Fig 2A). On a descriptive level, a higher reactivity could be observed for the LEARN task starting from approximately 3 seconds of the task interval. Oxy-Hb peaked around 6 to 8 seconds on average, while deoxy-Hb reached a maximal decrease starting from 8 seconds on. In contrast, the RANDOM and APPLY tasks were associated with a less pronounced and gradual signal change for oxy-Hb and almost no change for deoxy-Hb.

To better quantify these changes, we analyzed the difference between oxy- and deoxy-Hb (time window 6 to 12 s). This difference index has been shown to reflect cerebral blood flow and is often used in tasks involving motor responses [27,40]. A 3 x 3 repeated measures ANOVA indicated significant main effects for both within-subject factors TASK ($F(1,15) = 4.29$, $p < 0.05$, $\eta 2 = 0.22$) and ROI ($F(1,15) = 3.32$, $p < 0.05$, $\eta 2 = 0.18$). In particular, Hb-differences were higher during LEARN ($M = 0.082$, $SE = 0.014$ m(mol/l) x mm) when compared to RANDOM ($M = 0.048$, $SE = 0.015$) and APPLY ($M = 0.043$, $SE = 0.008$). The main effect ROI showed higher signal change over central sensorimotor area ($M = 0.071$, $SE = 0.009$) compared to the prefrontal ROI ($M = 0.047$, $SE = 0.011$). However, the interaction TASK x ROI was not significant ($F(1,15) = 1.06$, $p = 0.38$).

In a 'cost-benefit analysis' we then sought to combine the behavioral and physiological data and to assess the overall cognitive load during the task. To this end, we calculated the cumulative sum of objects caught within a block against the Hb-difference. This index thus shows the neuronal effort associated with each of the falling objects. Fig 2B reveals that an overall increased neuronal activation was necessary during the LEARN task to catch the falling objects. In particular, a steep increase of the curve after the sixth object could be observed that saturated for the last three objects only. In contrast, the load profile for the remaining two tasks was similar and showed a gradually increasing activation. This overall pattern of higher reactivity was evident for all three selected ROIs (S1 Fig).

Topographical plots of the average Hb-differences described statistically above corroborated an increased activation during LEARN over a broad cortical region (Fig 3A). The main focus was located over central sites extending to parietal and prefrontal regions. Similar albeit weaker

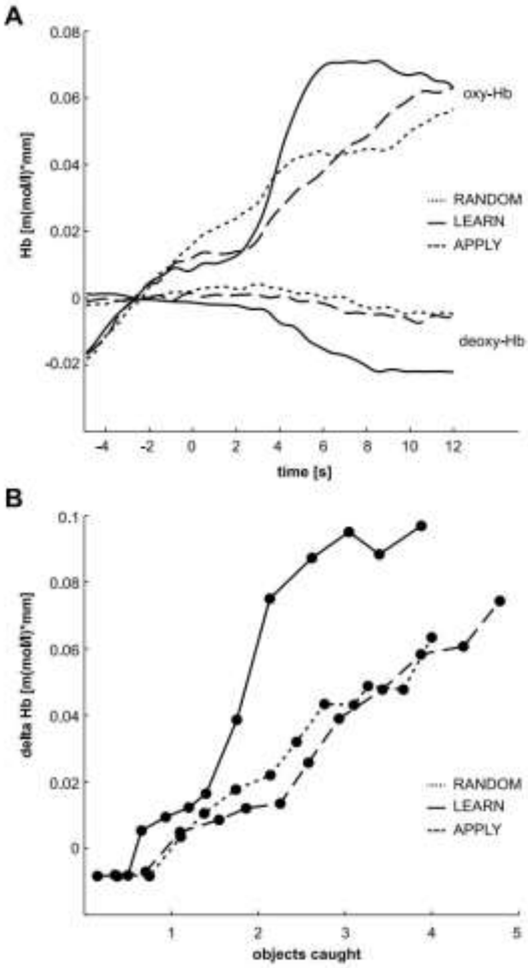

Fig 2. Average hemoglobin changes. (A) Changes of oxygenated (oxy) and deoxygenated (deoxy) hemoglobin (Hb) relative to a five second baseline for the three different tasks. The time courses represent a grand average over all channels and participants. Time point zero indicates the beginning of the game task. (B) Cost-benefit curves relating the grand average (over channels and participants) of the hemoglobin difference oxy-deoxy (delta Hb) to the cumulative number of objects caught. Each dot represents one of the twelve falling objects within a block. Note that delta Hb time series have been resampled.

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changes were found for the RANDOM task, with a focus over primary sensorimotor areas. In contrast, the maximum activations during the APPLY task were mostly confined to posterior parietal and dorsolateral prefrontal areas. Because these average activation plots can only represent a first hint on the main areas involved, multidimensional scaling was used to visualize the different networks both within and across tasks according to their neuronal similarity [44]. We decided to use correlation over time as an index of functional connectivity here. Similar approaches have been applied for example to identify language networks during speech comprehension [48]. Multidimensional scaling optimized the positions of single channels in a low-

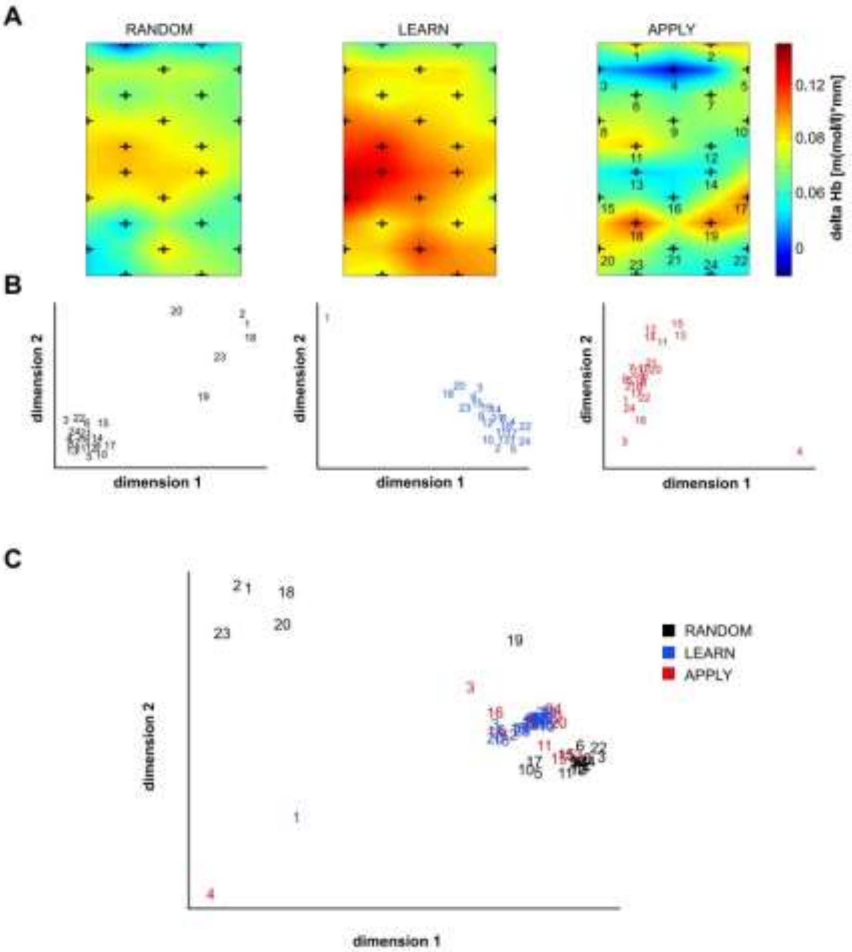

Fig 3. Topographical patterns. (A) Grand average topographies for the time period 6 to 12 seconds. Numbers indicate channels as shown in Fig 1. (B) Mapping of the activations (numbers again represent channels) to a two-dimensional space by multidimensional scaling. We used pairwise correlation between channels as input to an iterative procedure based on the smacof algorithm (for details see Methods). Channels with a high correlation will cluster together, thus revealing the structure of the whole network (stress values for RANDOM, LEARN and APPLY: 1.3, 1.0 and 0.6). (C) Same data as in (B) mapped into a common space (stress value: 0.003). Note that the resulting configuration dimensions are without a unit and lower stress values indicate a better fit.

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dimensional space to represent the overall 'similarity structure' of a higher dimensional space [49]. Fig 3B displays the resulting two-dimensional coordinates that represent the similarities based on the correlation between pairs of channels. The LEARN task was associated with basically one extended cluster. In contrast, two separate clusters covering mostly pre- and post-central or fronto-parietal regions were identified for the RANDOM task. For the APPLY task, channels over primary sensorimotor areas were grouped together and slightly stood out from the remaining channels. Within this second larger cluster, a subset of fronto-parietal channels (channels 1, 3, 16, 24) could be observed. In addition to these clusters within a given task, we also pooled the correlation matrices of all three tasks as input to multidimensional scaling. Besides the identification of fine patterns, this provided a global comparison of the connectivity patterns across tasks (Fig 3C). The analysis revealed a high similarity between the LEARN and APPLY tasks, while the RANDOM task showed an overall different configuration.

Discussion

In this study, we showed that different demands on cognitive control during gaming are reflected in changes of hemoglobin concentrations recorded with NIRS. An increased reactivity of NIRS signals over distributed areas including prefrontal, central and parietal brain regions could be observed when participants were required to extract simple stimulus-response mappings.

Gaming performance

Our gaming approach was designed to put high demands on players so that successful performance could only be reached when participants were able to infer and implement the correct stimulus-response mappings. This is confirmed by the finding that during APPLY success rates were clearly above chance. In this task, there was an improvement for the last block and the objects falling latest within a given block. Although the correct mapping was known in advance, this may indicate that participants were uncertain about these regularities in the beginning and needed some time to get used to the task. During RANDOM we observed chance-level performance and no significant trends over repetitions and objects. This most likely reflects the intended reaction task depending on fast motor responses only. In contrast, participants were more successful catching late objects within a block for the LEARN task. As the overall performance was not different from RANDOM and no trend over blocks was detectable, we attribute this behavior to the cognitive demands associated with extraction of the stimulus-response mappings: only from the third object on, a given mapping can be inferred and subsequently has to be validated and applied. This process has to be repeated for each new block and likely impedes a better performance in the brief high-speed game. The unexpected chance-level performance during LEARN therefore might reflect the highly demanding settings of the game. At the same time, these settings allowed avoiding learning effects due to mere task repetition and prevented participants from catching objects without extraction of the mappings. Moreover, most stimulus-response mappings were identified in the post-hoc questionnaires so that participants most likely focused on extraction of these regularities rather than catching the falling objects. Future studies with more objects falling within a block could help to assess the transition from extraction to application of a given mapping. In this line, past work [7] indicated that one-to-one mappings between stimulus and response result in a learning curve with gradually increasing performance taking around 90 trials to exceed the lower confidence bound.

Up-regulation of NIRS during gaming

Having shown behavioral differences, we next assessed the correlates in NIRS signals. The most distinct increase of reactivity for oxy- and deoxy-Hb was found only during the LEARN task. Further, the steep increase in oxy-Hb coincided with the time period when the hidden stimulus-response mappings could be discovered. As also illustrated by the cost-benefit curve, these results suggest an increased cognitive load when participants were required to extract unknown stimulus-response mappings. This is in line with past findings that have identified a network of brain areas specifically activated during initiation of cognitive control processes [15,16]. This network is supposed to respond to onset cues of the task and monitor feedback

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abilities are still remained for futher studies. Thus, investigation of computer games to fulfill the applicable knowledge to support the early intevention and therapetics of cognitve decline is needed.

The phenomena relating to affections and cognitions in neuronscience studies are understood through activities of brain signal such as electroencephalogram (EEG), functional magnetic resonance imaging (fMRI), and near-Infrared spectroscopy (NIRs). Emotion status was understood regarding the EEG signal patterns[7], while cognitive abilities among Alzheimer patients can be observed through MRI [8], [9]. Moreover, hemodynamic oxygenation changes via NIRs were also investigated during brain acitivities in patients [10]. Brain signals now provide promissing sources. It is believed to be an effective tool for monitoring brain activities during various mental tasks, entertainment actitvities and social events.

In this paper, we focus on the brain oxygenated hemoglobin signal during the mental tasks before and after playing a computer-based casual puzzle game. The computer-based puzzle game is addicitve and easy to play, at the same time, it provides dimensions for a player to activate more on his brain function. We hypothsize that the effects of playing computer games can be reflected through oxygenate hemodynamic of brain. Additionally, the casual puzzle game might improve performance of cognitve function. The cognitve domains investigated in this paper include cognitive flexibility via stroop task, visuo-spatial ability via mental rotation task, memory capacity via pair association task, and attention ability via finding difference task.

2 Method

2.1 Subject

The study initially recruited seven subjects. The subjects are students atJapan Advanced Institute of Science and Technology. They are considered as healthy subjects due to the non- clinical history related to brain, and neurological, psychiatric and cardiovascular disorders. The mean age of subjects is 27 ± 3.8 and three of all subjects are male.

2.2 Neuropsychological testing

Neuropsychological testing is one of performance-based methods to assess a wide range of cognitive functioning and ability. For neuropsycholoical test in this study, stroop task and mental rotation are used.

Stroop task was originally developed since 1993 [11]. It was used widely in various research purposes under cogntive psychology domain [14], [13]. The study recruits the stroop task to measure the perceptual processing speed ability. We use PsyToolkit "psytoolkit.org/" [15], [16] as a tool to demonstrate a computer-based stroop task experiement. Aside, mental rotation task, whose concept was first introduced in 1971 by Shepard and Metzler [17], was used to examinne the visuo-spatial ability of each subject before and after the puzzle game. Mental rotation task in this study is to rotate a mental representative of two dimentional objects.

Moreover, some additional tests of attention and memory were also taken. The additional memory test is an associated pair matching game. This game allows subjects five seconds to remember 9 position of 3 pairs of pictures. Then, the subject was asked to match each picture with its pair on a correct position. Another game for testing attention is finding different item among the group. The subject was given sets of pictures. The subject was required to pick a different picture among each set.

2.3 Optical topography fNIRs device

To observe changes of hemodynamic signal in the prefrontal cortex, we used fNIRs wearable optimal topography WOT 220, manufactored by HITACHI. The fNIRs allows us to observe both oxygenated heboglobin (Oxy-Hb), and deoxygenate hemoglobin (deoxy-Hb) blood flow in the cerebral prefrontal cortex. The mesurement consists of 22 chanals to capture the signals on the cortex. The fNIRs optical WOT 220 is non-invasive device, which is light weight and easy to wear on subject's head. The device supports the real-time monitoring on an event in which the subject can freely move his body during the experiement.

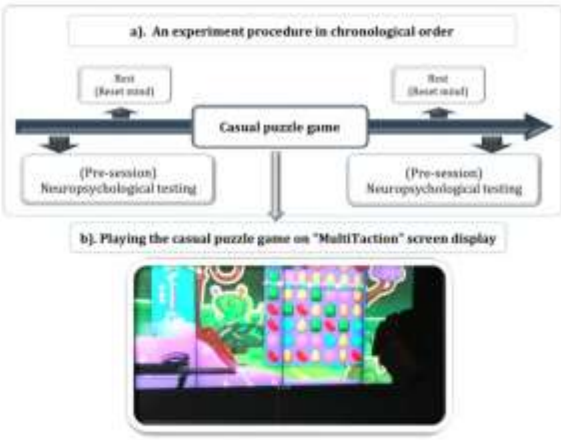

Fig. 1. An overview of experimental procedure

2.4 Experiemental procedure

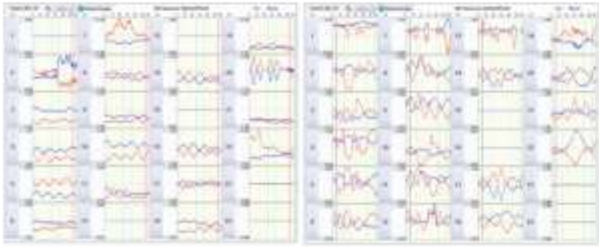

Fig. 2. Sample data of hemodynamic signal from subject B and subject E

After obtaining the consent, each subject was asked to wear the fNIRS device through the whole experiment, and sit in front of the computer display screen. During wearing fNIRs device, each subject was ensured not to lower and raised his head during each session in order to aviod noisy signals. As shown in picture a) of the Fig. 1, the experiement includes three main sessions: pre−neuropsychological test as a pre−session before the casual game playing, casual puzzle game playing, and post−neuropsychological test as a post−session after playing the casual puzzle game. The casual puzzle game used in this experment is "Candy Crush Soda Sugar". Each subject was asked to play this casual game for 20 minutes on "MultiTaction" device, the window operating system with 55-inch wide (16:9) Full HD 1920 x 1080 screen display as shown in picture b). of Fig. 1. Moreover, between each session during the experiment, the mind is reset by closing eyes and doing inhale−exhale for 3 rounds.

The experiement was hold in a specific room with a quiet environement, where there were only subjects and researcher.

3 Data Acquisition

3.1 Data of cerbral blood flow

With WOT-220 HITACHI device, the cerebral blood flow inclucing oxygenated and deoxygenated hemoblobin signals with 22-channels were retrieved. Some channels do not work well due to the intervention of hairs and other physical condition of each individual. As shown in the Fig. 2, the left-side picture shows the hemodynamic signals in cerebral prefontral cortex of subject B, in which the channel 1, 12 , 13, and 15 did not capture well the brain signals. The right-side picture of the Fig. 2 shows the hemodynamic signals of subject E, of which only channel 15 and channel 16 did not work well. The red lines indicate the changes of oxygenated hemoglobin (Oxy-Hb) on each channel, and the blue lines show deoxygenated hemoglobin (deoxy-Hb) of cerebal prefrontal cortex on each channel. This study, however, focuses only on oxy-Hb signals.

3.2 Normalization of oxy-Hb

In order to do a simply observation of the changes of signal between pre and post session of the casual game playing, we first implement the measurement by computing the median of the normalized oxy-Hb in both pre session and post session. The oxy-Hb signal in channel- n of subject i was nomrlized with max-min normalzation approach with the folllowing equation:

$$OxyHb'_{i_n} = \frac{OxyHb_{i_n} - min(i_n)}{max(i_n) + min(i_n)}$$

Where $min(i_n)$ is the minimum value and $max(i_n)$ is the maximum value of oxy-Hb signal in channel- n of subject i through each neuropsychological test session (pre-session and post-session).

Each signal is considered as a vector V that contains k component(with k length). The median value of each normalized signal was generated by sorting data component of each signal in ascending order and then, when k length is an odd number, the middle value of a signal is $\frac{(k+1)}{2}^{th}$. And, the median of a signal is computed by the average of two middle values, when k length is an even number.

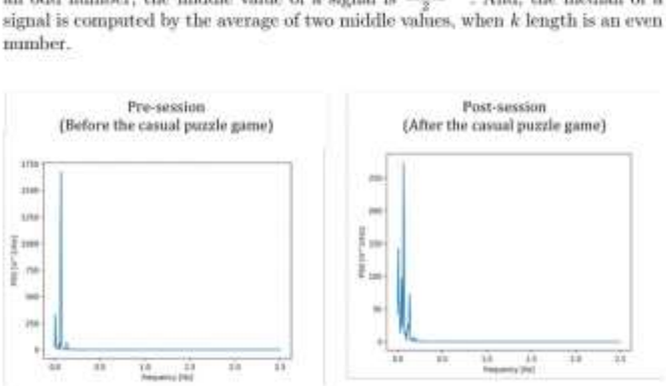

Fig. 3. The power spectral density of subject G during the mental tasks through neuropsychology testing before and after playing the casual puzzle game

3.3 Power spectral density

The power spectral density (PSD) is a point estimation of the energy variation in time series signal data as a frequency function. In this tstudy, we compute the PSD based on Welch's method [18]. The PSD is determined by averaging the windowed periodgram [19]. Regarding the Welch method, the original sequence signal is divided in multiple overlapping segments. Then, the welch method computes an array for each segment, in which each element is an average of the corresponding elements of all divided segments.

We computed PSD to extract maximum energy as the strongest variance of the oxy-Hb signal of each subject during the neurological testing in pre-session (before playing a casual puzzle game), and in the post session (after playing a casual puzzle game). We implemented on python with library SciPy. An example of the PSDs generated from oxy-Hb signal in channel 22 of subject G during his mental tasks in pre−session and post−session are shown in Fig. 3.

4 Result and discussion

4.1 Cognitive performance through neuropsychological testing

Fig. 4. Scores of neuropsychological testing

Fig. 4 shows the scores of neuropsychological testing. The results show that after a causal puzzle game playing, the ability of visuo-spatialization has been obviously improved, when the evidence through a mental rotation task shows the number of correct responses from each subject increased with less responding time (see top-right chart of Fig. 4). Similarly, stroop effect of each subject after enjoying the causal game was likely to be reduced. The score of stroop effects was computed by the average speed in correct trails of incongruent minus that in congruent. The smaller scores of stroop effect refer that individuals is faster in naming the color of ink a word is [22]. According to the top-left diagrame of Fig. 4, 60% of subjects produced lower stroop effects after playing the puzzle game. This phenomenon might refer that each control subject have the speed improvement of perceptual function after enjoying the casual puzzle game. In contrast, visaul attention ability through finding different picture was droped down. Meanwhile, the scores from experiemental result did show unstabe trends of memory performance through associated pair matching game task.

4.2 Oxy-Hb signal analysis

To illustrate the individual level, Fig. 5 shows the median values of the normalized oxy-Hb from 22-channels fNIRs for each subject during the mental tasks through neurolopsychological testing before and after playing a causal puzzle game. It is shown through the Fig. 5 that median value is missing from some channels due to the intervention of subjects' physical conditions. Thus, the common channels that well extacted hemodynamic signals from all subjects were considered to monitor the changes of brain activation in the population level.

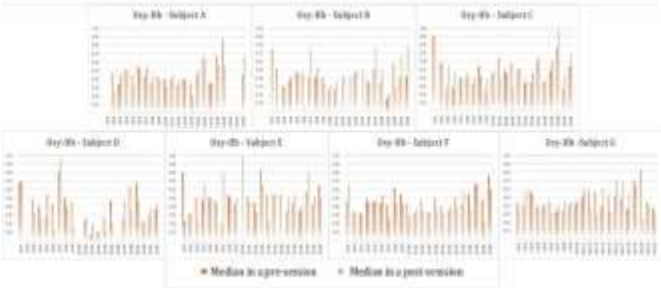

Fig. 5. Median of normalized oxy-Hb signals in 22-channel fNIRs by each subject

The channel 3, 9, 14, 19, and 22 are representatives to illustrate the changes of brain activation in this study. The change is generated by the middle values of normalized oxy-Hb signals after a causal game playing minus those before a game entertaining. The minus values of changes indicated that the medians of the normalized oxy-Hb signals after the casual game are smaller than those before the casual game as shown in the Fig. 6.

Fig. 6. Changes of brain activation through middle values of normalized oxy-Hb

The Fig. 6 shows an interesting results when all subjects excluding subject C have decreasing middle values of the normalized oxy-Hb.

Additionally, the power spectral density (PSD) of oxy-Hb signals also significantly changed after the casual game playing. The energy variation of oxy-Hb signals were reduced in the post-session, especailly, channel 19 shows a big difference of the strong varaince of oxy-Hb before and after the causal game playing.

Previous work through fNIRs-based signals indicated brain activations during a mental task of healthy control are higher than those in schizophrenic patients [21]. On the other hand, the study of observing mental workload through different levels induced the brain activations in middle and difficult level of mental tasks are higher than those in easy level [20]. In our case study with healthy control, the changes of oxygenated hemoglobin through middle values and PSD were slightly reduced while cognitive performance in mental rotation and stroop task were gradually improved.

The lower in PSD and middle values of oxy-Hb might induce the release of workload in brain function after the computer game entertainment. However, from the evidence of our experiment, indicating the correlation between oxy-Hb changes and cognitive performance is still in ambiguity. The PSD and middle values only indicated the changes of the brain activation before and after the computer casual game, while in order to clarify the relation between cognitive performance and oxygenated hemoglobin signals, the study requires larger number of samples. Moreover, our limitation in this study also related to the invetigation of fNIRs signals on four mental tasks without seperation on each task. Each mental task, for examaple mental rotation, stroop task, assiciated

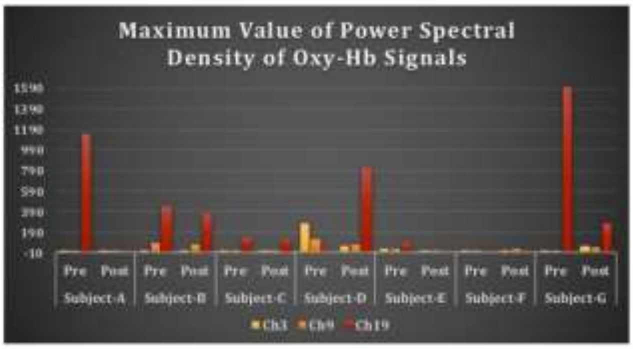

Fig. 7. Changes of brain activation through power spectral density

pair matching task as well as finding difference task, has its own charateristics, and might require different pattern of brain activation. If the oxy-Hb signals had been investigated in each signle mental task, the changes of oxy-Hb signals on a particular domain of cognitve performance would be obtained and more clearly explained.

5 Conclusion

In this paper, we investigated the cognitve performance before and after the entertainment through playing the casual puzzle game . We also investigated whether the brain activation is influenced by the casual puzzle game playing. The study suggessted that the casaul puzzle game in the form of computer version improve an immediate capacity of cogntive flexibility and visio-spatial ability, however, the short-term memory and fast eyes capacity are still in ambiguity. Moreover, the investigated features such as median of max-min normalized oxy-Hb and the power spectral density of oxygenated hemoglobin signal show the differentiation of brain activation in which oxy-Hb signals after a casual game playing have smaller variation comparing with those before the casual game. In order to infer the relation of oxygenated hemodynamic changes and the cognitve ability improvement, and understand the cognitive performance changes through oxy-Hb signals, we plan to extend our future study with larger population together with comprehensively investigate oxy-Hb signals on each type of cognitve ability, individually. Importantly, the advanced statistical machine learninig approach to interprete the changes of fNIRs oxy-Hb signals on cognitve performance is considered to be employed .

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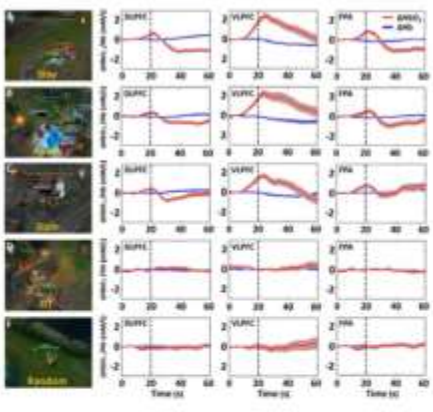
Real-time monitoring prefrontal activities during online video game playing by functional near-infrared spectroscopy

Yue Li[1,2], *Lei Zhang*[1], *Kehong Long*[2], *Hui Gong*[1,*], *Hao Lei*[1,2,*]

Author 1 and Author 2 contributed equally to this work.
[1] Wuhan National Laboratory for Optoelectronics, Huazhong University of Science and Technology, Wuhan 430074, P. R. China
[2] National Center for Magnetic Resonance in Wuhan, State Key Laboratory of Magnetic Resonance and Atomic and Molecular Physics, Wuhan Institute of Physics and Mathematics, Wuhan 430071, P.R. China

Key words: functional near-infrared spectroscopy, real-time monitoring, online video game, prefrontal cortex, event-related analysis

A growing body of literature has suggested that video game playing can induce functional and structural plasticity of the brain. The underlying mechanisms, however, remain poorly understood. In this study, functional near-infrared spectroscopy (fNIRS) was used to record prefrontal activities in 24 experienced game players when they played a massively multiplayer online battle arena (MOBA) video game, League of Legends (LOL), under naturalistic conditions. It was observed that game onset was associated with significant activations in the ventrolateral prefrontal cortex (VLPFC) and concomitant deactivations in the dorsolateral prefrontal cortex (DLPFC) and frontal pole area (FPA). Game events, such as slaying an enemy and being slain by an enemy evoked region-specific time-locked hemodynamic/oxygenation responses in the prefrontal cortex. It was proposed that the VLPFC activities during LOL playing are likely responses to visuo-motor task load of the game, while the DLPFC/FPA activities may be involved in the constant shifts of attentional states and allocation of cognitive resources required by game playing. The present study demonstrated that it is feasible to use fNIRS to monitor real-time prefrontal activity during online video game playing.



Game events-evoked hemoglobin concentration changes in the prefrontal cortex while playing League of Legends. Slaying an enemy (A), Assist (B), Being slain by an enemy (C), destroy a turret (DT, D) and an artificially constructed random condition (E).

1. Introduction

Video games are played for recreation, entertainment, training and rehabilitation purposes, and even as a sport. Many previous studies have demonstrated that video game training is associated with improvements in working memory, mental processing speed, multi-tasking, attentional control, and other cognitive abilities [1-6]. On the other hand, excessive video game playing or exposure to improper game contents, especially for school children and adolescences, may have negative effects, including poor performance and misconducts in

* Corresponding author: e-mail: leihao@wipm.ac.cn (H. Lei), huigong@mail.hust.edu.cn (H. Gong)

school [7, 8], increased propensity for violence or risky behaviors [8-10], poor decision-making ability [11], impaired impulsivity inhibition [12], emotion management problem [13], and even online game addiction (OGA) [14].

Many previous neuroimaging studies have demonstrated that video game playing induces functional and structural plasticity in the prefrontal cortex (PFC). In children, adolescence and young adults, the self-reported amount of video game playing correlated with cortical thickness of the left dorsolateral prefrontal cortex (DLPFC) [15] and microstructural properties of PFC white matters (WM) [16]. Longitudinal studies revealed that weeks to months of video game training altered functional activities, resting-state functional connectivity (FC), and gray matter (GM) volumes/cortical thickness of the DLPFC [17-20] and other brain regions such as the orbitofrontal cortex (OFC) [21] and striatum [18, 22]. OGA and general internet addiction were frequently reported to be associated with functional and structural abnormalities in the DLPFC, OFC, and anterior cingulate (ACC), as well as the WM tracts connecting to these regions [23-26].

The mechanisms underlying video game-related plastic brain changes remain unclear, and might be related to tonic/phasic activation or inhibition of the affected brain regions during game playing. Functional magnetic resonance imaging (fMRI) has been used to measure brain activities during video game playing and other real-world events such as movie watching [27-29]. However, performing such tasks, especially those complicated tasks that need strong engagement and extensive body movements, inside a scanner bore could be associated with significantly different brain activities from those would be obtained under naturalistic conditions. Moreover, most previous fMRI studies on video game playing used block design [30-32], and few such studies investigated the brain responses elicited by specific game events.

Electroencephalography (EEG) and functional near-infrared spectroscopy (fNIRS) have also been used to monitor brain activities associated with video game playing [33]. It has been demonstrated that it is feasible to use EEG to explore event-related neural processes during video game playing under naturalistic conditions [34-36]. Having a good compromise among temporal resolution, spatial resolution and ecological validity, fNIRS is already proven a useful tool to monitor time-resolved hemodynamic/oxygenation changes in the PFC and temporal gyrus during video game playing [37-39]. In this study, we used fNIRS to record real-time hemoglobin concentration changes in the PFC when the subjects played a massively multiplayer online battle arena (MOBA) video game, League of Legends (LOL). The aims are 1) to investigate whether it is feasible to use fNIRS to monitor real-time brain activities during MOBA game playing; and 2) to test the hypothesis that specific game events, such as slaying an enemy and being slain by an enemy, are associated with differential brain activities.

2. Methods

2.1 Subjects

The research was approved by the Human Subjects Institutional Review Board of Huazhong University of Science and Technology. All subjects were normal right-handed college students recruited on campus, all in good physical and mental conditions and having normal or corrected normal vision. All subjects played video games regularly, with a minimal playing time 5 hours per week, and 11.2 ± 6.3 hours per week on average. A total of 24 subjects (1 female, 18-23 years old, mean age 19.7 ± 1.4) participated the study.

2.2 fNIRS Data Collection

fNIRS data were collected using a homemade continuous-wave fNIRS instrument with 6 dual-wavelength (i.e., 850 and 785 nm) laser sources (S1-6), 24 regular detectors and 6 short distance detectors (N1-6) [40]. Each laser source was surrounded by 6 evenly distributed detectors (i.e., some of the detectors were multiplexed) and 1 short distance detector. The distance was 30 mm between the source-regular detector pairs, and 12 mm between the source-short distance detector pairs. Each source-regular detector pair formed an optical channel that measured hemoglobin signals from the brain region underneath. Each source-short distance detector formed a short channel that measured hemoglobin signals originated mainly from the shallow layers (i.e., scalp and skull) [41]. All sources and detectors were plugged into a custom-made probe cap, which was connected to the console via optical fibers.

The probe distribution on the cap followed the anatomical landmarks of international 10-20 system (Fig. 1). The laser sources S2/5 were put at the positions of electrodes F8/7, and S3/6 at the positions of Fp2/1. The laser sources S1/4 were placed near the location of the EEG electrodes F4/3, forming an equilateral triangle with the S2/5 and S3/6. In selected subjects (n=3), a tracking device (FASTRAK, Polhemus Inc., Colchester, VT) was used to obtain the exact locations of the channels on the scalp, the coordinates of which were then projected into the Montreal Neurological Institute (MNI) space to obtain their probabilistic distributions [42-44]. Based on the probability (p>0.95), we chose the channels 6/24, 9/27 and 18/36 to represent bilateral DLPFC, VLPFC and frontal pole area (FPA), respectively (Fig. 1C).

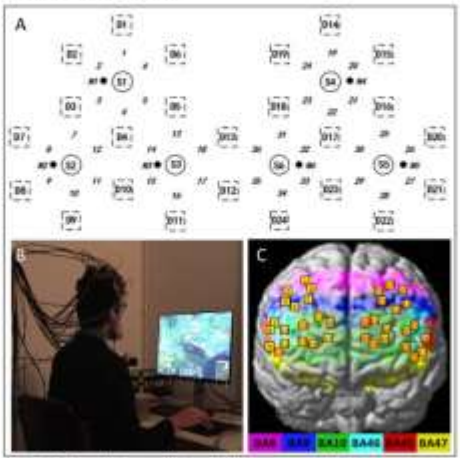


Fig. 1 Distribution of six light sources (S1-6), twenty four regular detectors (D1-24), six short-distance detectors (N1-6), 36 regular optical channels, and 6 short channels on the fNIRS cap (panel A). Panel B shows a photo depicting the experimental settings. Panel C shows projection of the regular optical channels on the surface of prefrontal cortex, on which the Brodmann areas (BA) are color-coded. The template was standard brain in MNI space provided by the SPM toolbox.

All data were collected at a sampling rate of 50 Hz. The raw data was first low-pass filtered (<3 Hz), before being converted into optical density (ΔOD). The data were then down-sampled to 10 Hz and converted into hemoglobin concentrations with the modified Beer-Lambert law [45]. In order to remove the interferences caused by heart beating, respiration and low-frequency signal drift, the hemoglobin signals were band-pass filtered with a frequency range of 0.015-0.2 Hz. Contamination signals from the scalp and skull, as well as shared component (such as systemic signals) that was contained in both the shallow layers and brain tissues, were removed using the multi-distance optodes and independent component analysis (MD-ICA) method [41].

2.3 Game

LOL was released in 2009, and is by far the most popular MOBA video game around the world [46]. All subjects had more than 1 year of experience playing this game. Only the players with similar gaming skill levels, determined by the built-in ranking system of League of Legends, were recruited. Twenty two subjects ranked the Silver Division in the game when they participated the study, and two ranked the Bronze Division. In this game, 10 online players are divided into 2 teams, and the members of each team control their own virtual characters, which are called champions, fighting with the opposing team in a fiction world. Each player exerts their gaming skills to pursue a final team victory by destroying the turrets and the base of the enemy team, while protecting his/her own. During the offensive and defensive processes, the champions can either slay or be slain. Slaying will reward the players with virtual gold and experience, which they can use to upgrade their characters; being slain will recall the champion back to the base to wait for resurgence. The players can recall their champions back to the base voluntarily to get replenished. The player can also slay the non-player-controlled characters or destroy the turrets of the enemy team to gain advantages. The game will not end until one team surrenders voluntarily or the base of one team is destroyed by the opponent. One round of game usually lasts 20-50 minutes. Due to the nature of the game, the player will have totally different and unpredictable gaming experience in each round of playing. More information of LOL can be found online at: http://na.leagueoflegends.com/en.

LOL has several game modes. The Matching mode is a mode in which online team mates and opponents in one round are selected by a matching algorithm on the server to ensure that all players have similar gaming skill levels and feeling of game difficulty. In the present study, each subject was required to play one round of matching mode LOL game in a sound-proof room, while wearing the fNIRS probe cap (Fig. 1B). The subjects were asked to look at the loading screen silently for 20 s before the game onset. fNIRS data were recorded continuously during this period and throughout the actual game play. A built-in software was used to record the video data of the game playing at 15 frames/s. After the game, the participants were asked to rate their gaming experiences by answering the following three questions: 1) How do you feel when you slay an enemy in the game? 2) How do you feel when you assist your teammate to slay an enemy? 3) How do you feel when you were slain in the game? A 5-point score system was used for the responses: 1-very unhappy; 2-unhappy; 3-normal; 4-happy; 5-very happy.

2.4 Data analysis

The fNIRS data were analysed at two levels. First, we used a block-design approach to study the oxyhemoglobin (HbO_2) and deoxyhemoglobin (Hb) concentration changes associated with the game onset. For each player, the HbO_2/Hb measurements during the pre-game period were averaged to yield a baseline value, which were subtracted from the complete HbO_2/Hb time series. The normalized time series were then averaged across different players. The amplitudes of relative HbO_2/Hb changes ($\Delta HbO_2/\Delta Hb$) in three time windows were calculated and compared statistically using pair-wise Welch's unequal variances t-tests, followed by Bonferroni corrections for multiple comparisons. The three time windows selected were: 1) the pre-game period (i.e., 0-20 s); 2) between the game onset and the first encounter with an enemy champion (i.e., 50-90 s); and 3) after the first encounter with an enemy champion (i.e., 280-320 s). Topographic mapping of the HbO_2 and Hb concentrations during these time windows were obtained using cubic interpolation of the data recorded in all 36 regular channels [47].

At the second level, an event-related approach [34] was employed to analyse brain activities associated with specific game events. The video recording of each round of game playing was analysed by 2 experienced LOL players independently to tag the time point when any one of the following four events occurred: 1) the player slew a player-controlled champion from the enemy team (Slay); 2) the player assisted his/her teammates to slay a champion from the enemy team (Assist); 3) the player controlled champion was slain by the enemy team (Slain); 4) the player destroyed a turret of the enemy team (DT). There was a text message displayed on the computer screen whenever these events took place, together with a sound reminder. The analysts reviewed the footages frame by frame, and marked the beginning time point of each event with an uncertainty within ± 1 s. Differences between the analysts were resolved by double-checking and discussion until they came into an agreement. The total of number of the events tagged were Slay 110, Assist 72, Slain 98 and DT 60 (e.g., Slay 1-11, Assist 0-8, Slain 1-14, DT 0-8 for each player).

For each tagged game event, the fNIRS data recorded 20 s before and 40 s after the event were clipped. The averaged HbO_2/Hb level of the first 10 s of each data clip was used as the baseline to normalize the complete clip time series. For each event, the normalized clip time series were averaged within each player and across different players. The final averaged time series were considered to represent the time-locked HbO_2/Hb responses specific to these events. As control, a random event (Random) was constructed artificially. From the fNIRS time series of each player, N_{slay} pieces of 60 s-long clips were selected randomly by a computer and normalized individually as described previously for the other events, where N_{slay} was the number of Slay the player had. The time series of these normalized randomly selected clips were averaged, and the result was considered to represent the brain responses unspecific to any particular game event. Finally, the averaged HbO_2/Hb time series associated with different events were down-sampled to 1 Hz before being entered into statistical analysis. The down-sampled time series associated with Slay, Assist, Slain and DT were first compared with that associated with Random with repeat measures analysis of variance (ANOVA) to assess the main effect of event $\times$ time interaction. The events showed statistically significant event × time interaction (i.e., Slay, Assist and Slain) with Random were compared subsequently among themselves with repeat measures ANOVA. The amplitudes of ΔHbO_2 in three 4 s-long time windows were then calculated, and compared to the baselines statistically using one-sample t-test and among the events using one-way ANOVA. For each brain region and each time window, post hoc Bonferroni corrections were applied for multiple comparisons among the three events. The three selected time windows were: 1) the period with maximal time-locked activations (i.e., 21-24 s for the DLPFC and FPA, 23-26 s for the VLPFC); 2) 10-14 s after the occurrence of these events (i.e., 30-33 s); and 3) the last 4 s of the 60 s-long clips (i.e., 57-60 s).

For all data analyses described above, the data in the mirror channels in the two hemispheres were pooled together and used to represent the brain region of interest, after confirming that under no circumstances the responses were significantly lateralized. A corrected $p<0.05$ was considered statistically significant.

3. Results

The HbO_2 and Hb responses to the game onset (black dashed lines) are shown in Fig. 2. The DLPFC and FPA showed abrupt and statistically significant HbO_2 decreases upon the game onset, while the VLPFC had a significant HbO_2 increase (Fig. 2B). Upon the game onset, the Hb concentration increased significantly in the DLPFC, decreased significantly in the VLPFC, but had no significant changes in the FPA (Fig. 2C). The blue dashed lines and shades indicate the mean and standard deviation, respectively, of the time point of first encounter with an enemy champion (i.e., 123 ± 30 s). The HbO_2/Hb levels in the DLPFC returned gradually to the baseline after the first encounter. In comparison, the HbO_2 level in the FPA remained below the baseline after the first encounter, accompanied by a gradually decreased Hb level (Fig. 2B and C). The first enemy champion encounter evoked further HbO_2 increases and Hb decreases in the VLPFC, and such changes tended to level off around 100 s after the encounter (Fig. 2A-C). Figure 3 displays topographic mapping of the averaged HbO_2 and Hb concetrations during the three time windows selected.

Figure 4 shows screenshots of the Slay, Slain, Assist, DT and Random events, as well as the corresponding event-related HbO_2/Hb time series. The dashed black lines indicate the moment when the events occur. DT and Random appeared to have not evoked any time-locked responses, and the HbO_2/Hb signals only fluctuated around the baseline. In contrast, Slay, Assist and Slain were clearly associated with brain region-specific time-locked HbO_2 responses. For each of the three brain regions, statistically significant event × time interactions were observed when comparing the HbO_2 time series associated with Slay, Assist and Slain with that associated with Random. Pairwise comparisons among Slay, Assist and Slain were then conducted. For Slay vs. Slain and Assist vs. Slain comparisons, the event × time interaction was statistically significant in the DLPFC and FPA ($p<0.05$, with Bonferroni correction). For Slay vs. Assist comparison, the event × time interaction was statistically significant only in the FPA ($p<0.05$, with Bonferroni correction). It therefore appeared that the time-locked HbO_2 responses in the FPA were distinctive among Slay, Assist and Slain, while those in the VLPFC were similar. The time-locked HbO_2 responses in the DLPFC associated with Slay and Assist were similar, but significantly different from that associated with Slain.

Slay, Assist and Slain were all associated with a transient and significant HbO_2 increase in the DLPFC, VLPFC and FPA. Interestingly, the increases all started before the event onsets. On average, peak activation levels were reached within 2 s after the events in the DLPFC and FPA, and around 4 s in the VLPFC, followed by returns to the baselines. For each brain region, the averaged peak amplitudes of these transient increases were similar among the three events (Fig. 5). For all three events, the relative HbO_2 level in the VLPFC returned to the baselines by the end of the 60s time window. The relative HbO_2 levels in the DLPFC and FPA showed significant undershoots after Slay and Assist, which started to level off around 20 s after the event, and remained significantly below the baseline (Figs. 4A/B and 5). The relative HbO_2 level in the DLPFC had a post-event undershoot after Slain, which, however, started to recover about 10 s after the event, and reached the baseline level by the end of the 60s time window (Figs. 4C and 5). The relative HbO_2 level in the FPA had no significant undershoot after Slain. Instead, it remained at the baseline level for a period of time, followed by a significant increase (Figs. 4C and 5). No significant correlations were found between fNIRS responses to these game events and the game experiences assessed after playing (data not shown).

4. Discussion

The present study used fNIRS to record real-time PFC activities associated with MOBA game playing. It was shown that 1) the game onset was associated with abrupt and significant activations in the VLPFC and concomitant deactivations in the DLPFC and FPA; 2) the HbO_2 level in the VLPFC and DLPFC, but not in the FPA, increased significantly upon the first encounter with an enemy champion; 3) certain game events, including Slay, Assist and Slain, evoked distinctive time-locked HbO_2/Hb responses in the DLPFC and FPA, while the HbO_2/Hb responses in the VLPFC were similar across these events.

4.1 Time-locked Signal Averaging

Most of the previous functional neuroimaging studies on video game playing used block-design [30, 31, 48], and only few studies used event-related design [27, 49]. One technical difficulty in using event-related approaches to study brain activities associated with video game playing is how to define the game events. Advanced algorithms have been proposed to extract meaningful functional events from fNIRS-recorded data [50]. In this study, we chose to define the functional game events operationally, and the brain responses to such operationally-defined events, such as first encounter, Slay, and Slain, were analysed. This is inspired by a recent study which showed that certain events in video games could evoke time-locked EEG signals that were comparable to canonical event-related potential (ERP) components [34].

Video game playing is a real world task, and each round of game playing is unique and unrepeatable. An operationally-define event thus could occur under different contexts, and therefore evoke/induce different physiological/neural responses. As a result, the raw event-related fNIRS data are quite "noisy", containing both event-evoked components with fixed latency (i.e., time-locked) and event-induced components with jitter in latency, as well as other randomly occurring components not related to the event. To overcome this problem, we adopted the time-locked event-related signal averaging strategy originally developed for ERP recording to enhance only the time-locked component, while suppressing the other components [51, 52].

Time-locked prefrontal activation patterns were observed for functional events such as game onset, first encounter with an enemy champion, Slay, Assist and Slain. In comparison, signal averaging across the data segments recorded in randomly selected time windows resulted in no meaningful signals. Interestingly, time-locked signal averaging yielded no clear activation pattern for the DT event, implying that DT might not be salient enough to evoke coherent neural responses that were observable to this data processing method.

4.2 VLPFC Activities

VLPFC is involved in integration of multi-sensory stimuli, processing visual-object signals, spatial navigation and associating the results from these processes to motor responses and/or action control [39, 53, 54]. In addition, VLPFC is also a part of the ventral attentional network responsible for reorienting attention in a bottom-up manner when salient stimuli occur in the external environment [55]. VLPFC activations have been observed previously during video game playing and virtual reality tasks, and been linked to cognitive demand required for the player's visuo-motor interactions with the virtual environment [37, 39, 56].

In LOL, the player would be engaged with the game world immediately after the game onset. During the first two minutes or so, however, there was no enemy on the screen. For an experienced player, all he/she needs to do is to make some initial preparations, and simply move the champion to the battle front, thus requiring only little visuo-motor interactions. After the first encounter with an enemy champion, the player would be engaged into battles and fights, voluntarily or being forced to. The player would have to either try to slay an enemy champion or to assist his/her teammates to slay an enemy, or to escape from the battle scene, while avoiding being slain. To do so, he/she would need to process real-time visual/auditory information from the battle scene and exert his/her gaming skills rapidly and frequently.

The changes of HbO_2/Hb level in the VLPFC appeared to have followed the demand of visuo-motor interactions, being modest upon the game onset and becoming larger after the first encounter. The results are therefore consistent with the notion that VLPFC activations during video game playing may be a response to visuo-motor processes [39, 56].

This interpretation is also consistent with the VLPFC activation patterns observed for the Slay, Assist and Slain events. There would always be a fierce fight before these events, demanding more visuo-motor interactions, relative to those required at a non-fighting situation. The fight ended at the moment when any of the three events occurred, turning the game into a slow pace, just like the situation before the fight. The time-locked VLPFC activations would therefore most likely be responses to the initiation and termination of the fighting epochs preceding these events. Unlike Slay and Assist, after which the play would continue, Slain would immediately recall the player's champion into the nexus until resurgence. The more rapid post-event subsidence of VLPFC activation for Slain was consistent with the notion that waiting for resurgence in the nexus would need less visuo-motor interactions than continuing to play on the battle ground.

4.3 DLPFC Activities

The DLPFC is commonly considered as a node in the fronto-parietal control network supporting top-down cognitive control [57]. Early studies reported positive DLPFC activation during game-like cognitive tasks, which was modulated by game difficulty [58]. However, there are also many previous studies reporting DLPFC deactivations during virtual reality visuo-motor tasks and active video game playing [37-39, 59]. The deactivation of DLPFC appeared to be modulated by the genre of the game, but not the age or the performance level of the player [60]. Flow experience during video game playing, but not passive viewing of video game contents [59], was associated with DLPFC deactivations [56]. Consistent with these previous results, our results demonstrated that game onset was associated with an abrupt and significant deactivation of DLPFC, which subsequently returned towards the baseline after the first encounter with an enemy champion.

The reasons why DLPFC could become deactivated during virtual reality visuo-motor tasks/video game playing are still poorly understood, and remain a subject of debate [60]. It has been proposed that lateral PFC could be activated in common during rest, and the recruitment of lateral PFC during rest supports higher cognitive functions that would occur in specific tasks, such as visual imaginary and memory retrieval [61]. It has been consistently shown that DLPFC is activated during certain internally directed cognition (IDC) tasks such as mind wandering [62]. Deactivations of DLPFC were also often observed during automatic processes, such as spontaneous motor-action execution [63], creative thinking [64] and rapid eye movement sleep [65]. Consistent with the above observations, practice and development of automaticity were shown to decrease task-induced DLPFC activations [66].

In this study, the players were given no specific instruction/requirement regarding what to do before the game started. As such, the pre-game period could be viewed as a "resting" or "mind-wandering" period, during which the DLPFC could be activated. Little salient external stimuli were present on the battel ground during the first few minutes into the game play. For an experienced player, most of the motor actions could be executed automatically during this period, without any demand for deliberate externally directed cognition (EDC) and/or IDC processes [67]. Under such circumstance, the DLPFC activities might actually decease, relative to the level observed during the pre-game "resting" period. The real battle started after the first encounter, and the cognitive demand would increase considerably for the player, involving selective visuospatial attention, deliberate motor-action control and goal-directed IDC processes such as voluntarily planning for future, simulating future events in mind and voluntary episodic memory retrieval. All these cognitive processes, whether externally or internally directed, would activate DLPFC [68-70].

Interestingly, the Slay, Assist and Slain events were associated with time-locked DLPFC activations, which had similar amplitudes and all initiated about 10 s prior to the events. The activations subsided 2-4 s after the

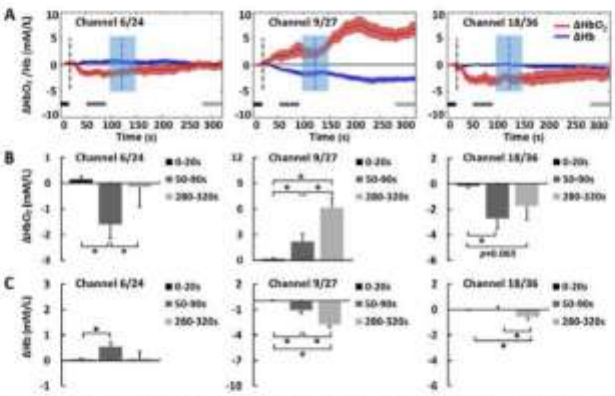


Fig. 2 HbO_2/Hb responses to game onset and first encounter with an enemy champion (A). The red solid lines and shades indicated the means and standard errors of the relative HbO_2 concentration changes. The blue solid lines and shades indicated the means and standard errors of the relative Hb concentration changes. The black dashed lines indicate the game onset. The blue dashed lines and shades indicate the mean and standard deviation of the time point (123 ± 30 s) of first encounter. The data in channel 6/24, channel 9/27 and channel 18/36 were chosen to represent the responses in bilateral dorsolateral prefrontal cortex (DLPFC), bilateral ventrolateral prefrontal cortex (VLPFC) and bilateral frontal pole area (FPA), respectively. Quantitative measurements of the averaged relative signal amplitude ($\Delta HbO_2/\Delta Hb$) were made in three time windows, indicated by the bars above the abscissa axis in (A). Black: the pre-game period, 0-20 s; dark gray: between the game onset and the first encounter, 50-90 s; light gray: after the first encounter, 280-320 s. ΔHbO_2 and ΔHb amplitudes were compared statistically in (B) and (C), respectively. $^*p < 0.05$, Welch's unequal variance t-test, followed by Bonferroni corrections. Error bars in (B) and (C) indicate standard errors.

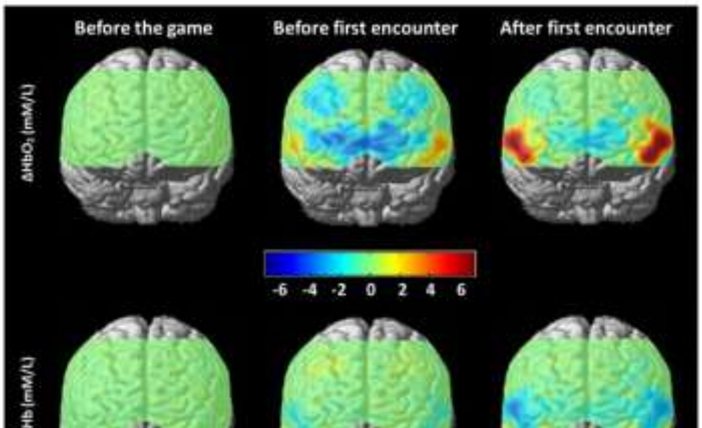


Fig. 3 Topographic mapping of relative HbO_2 and Hb concentrations during pre-game period (left column), between game onset and first encounter with an enemy champion (middle column) and after first encounter (right column). The template was standard brain in MNI space provided by the SPM toolbox.

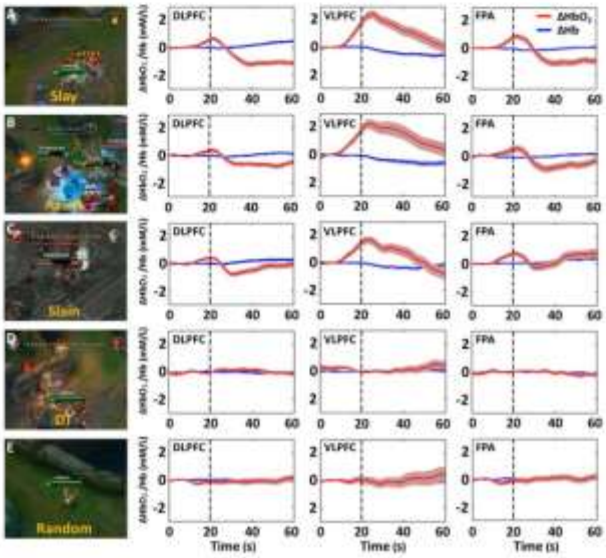


Fig. 4 Event-related time-locked HbO_2/Hb responses to Slay (A), Assist (B), Slain (C), destroy a turret (DT, D) and an artificially constructed random condition (E). Screenshots of these events were shown in the leftmost column. The red solid lines and shades indicated the means and standard errors of the relative HbO_2 concentration changes. The blue solid lines and shades indicated the means and standard errors of the relative Hb concentration changes. The back dashed lines indicated the time point when the events occurred.

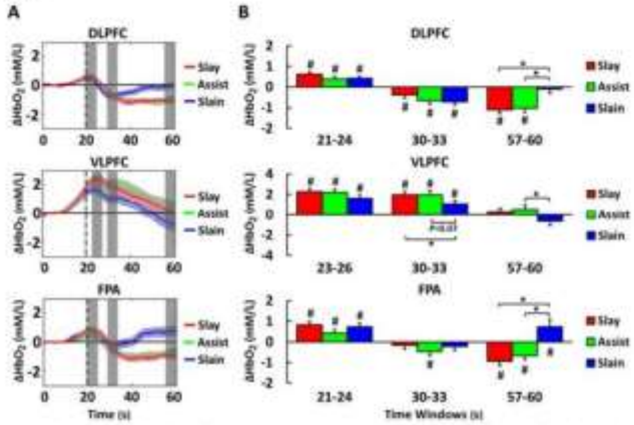


Fig. 5 Comparisons among the event-related HbO_2 responses to Slay, Assist and Slain. The HbO_2 time series associated with the three game events were plotted together in a brain-region specific manner (A). The colored solid lines and shades in (A) indicate the averages and standard errors of HbO_2 time series associated with Slay (red), Assist (green) and Slain (blue). The mean ΔHbO_2 amplitudes across three 4 s-long time windows (depicted by gray shades in (A)) were compared among different events (B). #$p < 0.05$, one-sample t-test, followed by Bonferroni corrections. *$p < 0.05$, one-way ANOVA, followed by post hoc Bonferroni corrections. Error bars in (B) indicate standard errors.

events, followed by HbO_2 undershoots indicating DLPFC deactivations. Similar to the case of VLPFC, the transient event-related DLPFC activations may reflect cognitive load increases (i.e., more selective attention and motor-action control) demanded by the preceding fight. After these events, the game would return to a relatively slower pace, and the player might also recover from the fully-immersed fighting state, and turned momentarily into a relatively more relaxed state until the next battle began. The post-event period might therefore be viewed as a time during which the demand for EDC was reduced, and the IDC processes would emerge and become more resilient, to some extent comparable to the period before the first encounter.

The post-event HbO_2 responses to Slain were different from those to Slay and Assist, in that the HbO_2 undershoot recovered to the baseline level 20-30 s after the event. As discussed previously, the player would continue to play after Slay and Assist, but be suspended from playing after Slain. Since no motor-actions could be executed while waiting in the nexus for resurgence, most of the players would view the battle scenes passively or "thinking" of how to play next during this period of time. Compared to active playing, staying in the nexus would require far less EDC processes, and as such many deliberate IDC processes could occur. In a sense, the time in the nexus was similar to the pre-game "resting" period, during which the DLPFC activity would increase due to internally directed higher cognitive functions.

All above discussions attributed the DLPFC activities during video game playing to its role in cognitive control. However, the existence of alternative interpretations could not be ignored. For instance, working memory is constantly required during video game playing, and may lead to DLPFC activations [71]. DLPFC activities could be recruited during fighting epochs to encode the reward prediction error signals [72]. Stress reactions to the extensive audio-visual stimuli in the game world could also contribute the inhibition of DLPFC [73]. Furthermore, video game playing is associated with elevated striatal dopamine release [74], which may modulate the activities of the DLPFC [75].

4.4 FPA Activities

The functions of PFC are organized in a gradient hierarchy, with increasing abstraction and complexity from the caudal part to the rostral part [76]. Being the most rostral region of the PFC, the FPA is thought to support complex cognitive process such as multitasking, high level goal maintenance and social cognition [77]. FPA activities during video game playing have been attributed to maintaining the internal goals [56] and compensating for the insufficient ability of more primary regions in processing visuo-motor tasks [37]. In this study, the FPA showed largely similar, but not identical, brain activities with the DLPFC. For example, on average the FPA showed significantly reduced HbO_2 and Hb levels during game play (Fig. 2), indicative of reduced regional cerebral blood flow and oxygen consumption relative to the baselines before the game onset. Such deactivations were not observed in the DLPFC.

The FPA is a heterogeneous region which could be divided into two or three subregions based on functional and structural connectivities; with the lateral part being more connected with the DLPFC, and the medial part being more connected with the default mode network (DMN) [78, 79]. One possible explanation for the FPA activity pattern observed in this study is that the fNIRS signals of this region contained contributions from both the lateral and medial subregions, correlated with the activities in the DLPFC and DMN, respectively. The DMN is deactivated during a wide variety of goal-directed behaviors [80], and exhibits negative correlation with the FPA/DLPFC during many top-down cognitive control tasks [81]. On the other hand, the DMN shows positively correlated activation with the FPA/DLPFC under more spontaneous situations, such as rest and mind wandering [67]. The maintained deactivation of FPA after the first encounter might result from the cognitive task-related inhibition of the DMN. The activation of FPA during the resurgence period after Slain might imply the activation of the DMN during this period.

4.5 Relevance to Game-related Brain Plasticity

It is shown in this study that online video game playing is associated with both tonic and phasic changes in prefrontal activities, which might contribute to the game-induced brain plasticity observed previously. For example, the VLPFC showed tonic activations during game playing, which might underpin improved visuo-motor capabilities in the frequent game players [82] and motor learning in the virtual environment [83]. The tonic deactivations in the FPA and phasic deactivations of the DLPFC, especially those associated with the rewarding events such as Slay and Assist, could underlie the reinforcement schedule of the game [84]. Nevertheless, further studies are required to clarify how the prefrontal activities change with video game training and whether the development of OGA is associated with plasticity in real-time prefrontal activities during game playing.

4.6 Limitations

There are several limitations in this study. First, although the MD-ICA method was used to reduce the signals from the shallow layers and systemic signals that were common for the shallow layers and brain tissues [41], it could not be guaranteed that the results reported were free of unspecific signals attributable to systematic arousal. Video game playing is associated with dynamic changes in arousal state [85]. Whether and how much the event-related prefrontal activities observed in the study were due to changes in general physiological arousal state need further investigation. One possible method is to record the heart rate, blood pressure and skin conductance simultaneously with fNIRS, and use these measurements to regress out the contribution from general arousal. Alternatively, more sophisticated artefact-reducing approaches could be used, such as removal of global components either derived from resting state data [86] or by principle component spatial filtering [87]. Secondly, it is generally believed that the HbO_2 data contain more physiological noises, and the Hb data is relatively more accurate in reflecting neural activities [88]. Under most circumstances in this study, the averaged Hb responses correlated negatively to the averaged HbO_2 response. However, exceptions were also observed (i.e., the FPA responses shown in Fig. 2A). The exact relationship among neural activities, hemodynamic changes and oxygenation changes are complicated and still not fully understood [89]. In this study, data interpretation was mainly based on HbO_2 measurements, due to their high SNR. Further studies are necessary to clarify the relationships between hemodynamic changes and oxygenation changes in the prefrontal cortex during video game playing. Last but not least, all subjects participated in the study were of similar game skill levels. It has already been demonstrated that the prefrontal activities associated with game playing are modulated by performance level and experiment conditions [37]. It is therefore noteworthy to point out that the event-related prefrontal activities observed in this study may only be specific to this particular group of players, and could not be generalized to players of different performance levels. It would be interesting to investigate in future how video game playing-evoked prefrontal activities change with the gaming skill level and along the course of game training.

Conclusions

During LOL playing, the game onset, first encounter with an enemy champion, as well as specific game events such as Slay, Assist and Slain, could evoke region-specific time-locked HbO_2/Hb responses in the PFC. The prefrontal activities associated with online video game playing exhibited both similarity with and differences from those observed during laboratory visuo-motor tasks. The VLPFC activities during video game playing most likely represents the visuo-motor task load, while the DLPFC/FPA activities may be involved in higher functions such as the shift of attentional states and allocation of cognitive resources. The study demonstrates that, under naturalistic settings, it is feasible to use fNIRS to monitor prefrontal activities in real time during online video game playing.

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