Die funktionelle Nah-Infrarot-Spektroskopie (fNIRS) und das visuell-räumliche Arbeitsgedächtnis: Experimentelle Befunde zur Sensitivität und Spezifität der Methode und zu intelligenzbedingten, interindividuellen Unterschieden der funktionellen Hirnaktivität

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Inhalt

Die vorliegende Dissertation beinhaltet zwei wissenschaftliche Artikel sowie ein Mantelpapier, welches eine Erläuterung zu den Artikeln darstellt.

Mantelpapier

Die funktionelle Nah-Infrarot-Spektroskopie (fNIRS) und das visuell-räumliche Arbeitsgedächtnis: Experimentelle Befunde zur Sensitivität und Spezifität der Methode und zu intelligenzbedingten, interindividuellen Unterschieden der funktionellen Hirnaktivität.

Studie 1

Witmer, J. S., Aeschlimann, E. A., Metz, A. J., Troche S. J. & Rammsayer, T. H. (2018a). The validity of functional near-infrared spectroscopy recordings of visuospatial working memory processes in humans. *Brain Sciences*, 8, 62; doi:10.3390/brainsci8040062

Studie 2

Witmer, J. S., Aeschlimann, E. A., Metz, A. J., Troche, S. J. & Rammsayer, T. H. (2018b). Functional near-infrared spectroscopy recordings of visuospatial working memory processes. Part II: a replication study in children on sensitivity and mental ability-induced differences in functional activation. *Brain Sciences,* 8, 152; doi:10.3390/brainsci8080152

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ÜBERBLICK

Das Ziel der vorliegenden Dissertation ist die Überprüfung, ob die funktionelle Nah-Infrarot-Spektroskopie (fNIRS) ausreichend sensitiv und spezifisch ist, um differenzierte Fragestellungen der Arbeitsgedächtnisforschung zu untersuchen und um intelligenzbedingte Unterschiede in der funktionellen Hirnaktivität nachzuweisen.

Im Vergleich zur Positronen-Emissions-Tomografie (PET), Einzelphotonen-Emissionscomputertomografie (SPECT) und funktionellen Magnetresonanztomografie (fMRI) ist die fNIRS ein relativ junges Bildgebungsverfahren, das aufgrund der tiefen Kosten, benutzerfreundlichen Anwendung und in die Messgeräte integrierten Auswertungsprogrammen in den letzten Jahren immer öfter zur Untersuchung verschiedenster Fragestellungen im Bereich der Neurowissenschaften, Psychologie und Psychiatrie eingesetzt wurde (Boas, Elwell, Ferrari & Taga, 2014). Obwohl die Grundprinzipien des Verfahrens seit mehr als 40 Jahren bekannt sind (Jöbsis, 1977) existieren bisher keine breit abgestützten und standardisierten Vorgehensweisen bezüglich der Signalverarbeitung (Pfeifer, Scholkmann & Labruyère, 2018). Da fMRI- im Vergleich zu fNIRS-Studien in viel grösserer Zahl vorliegen und das Signal beider Methoden auf der Hämoglobin Oxygenierung basiert, werden die Ergebnisse der beiden Methoden oft verglichen. So zeigten einige in den letzten Jahren durchgeführten Studien, dass das Signal des oxygenierten Hämoglobins (O_2Hb) der fNIRS mit dem Blood-Oxygenation-Level-Dependent (BOLD)-Signal der fMRI im frontalen und parietalen Kortex während der Bearbeitung visuell-räumlicher Arbeitsgedächtnisaufgaben signifikant positiv korreliert ist (zwischen r = .26 und r =. 86) (Cui, Bray, Bryant, Glover & Reiss, 2011; Sato et al., 2013; Wijeakumar, Huppert, Magnotta, Buss & Spencer, 2017). Auch der gut etablierte fMRI Befund, dass höhere Aufgabenanforderungen in Arbeitsgedächtnisaufgaben mit einer Zunahme der funktionellen Hirnaktivität im frontalen Kortex einhergehen (Todd & Marois, 2004) wurde in zahlreichen fNIRS Studien repliziert (Ayaz et al., 2012; Causse, Chua, Peysakhovich, Del Campo & Matton, 2017; Fishburn, Norr, Medvedev & Vaidya, 2014; Herff et al., 2014; Li, Luo & Gong, 2010; Molteni

et al., 2012; Wijeakumar et al., 2017). Daraus lässt sich schliessen, dass fNIRS ausreichend sensitiv ist, um unterschiedliche Aufgabenanforderungen in Arbeitsgedächtnisaufgaben abzubilden. Aufbauend auf diesem Befund war ein erstes Ziel der vorliegenden Studien (Witmer, Aeschlimann, Metz, Troche & Rammsayer, 2018a, 2018b), zu prüfen, ob fNIRS auch ausreichend sensitiv ist um ganz spezifische, visuell-räumliche Arbeitsgedächtnisprozesse abzubilden.

Zusätzlich wurde untersucht, ob intelligenzbedingte Unterschiede in der funktionellen Aktivität des Kortex auch mit fNIRS nachweisbar sind. Ebensolche Unterschiede wurden bisher in mehreren PET- (Haier et al., 1988; Parks et al., 1988) und fMRI-Studien (Basten, Stelzel & Fiebach, 2013; Lee et al., 2006) gefunden. Die Ergebnisse dieser Studien waren jedoch hinsichtlich der Richtung des Effekts heterogen. So berichteten beispielsweise Haier et al. (1988) und Parks et al. (1988) einen negativen Zusammenhang zwischen Intelligenz und kortikaler Aktivität, während Ebisch et al. (2012) und Basten et al. (2013) einen positiven Zusammenhang fanden. Mittels fNIRS wurden intelligenzbedingte Unterschiede der funktionellen Hirnaktivität erstmals von Di Domenico, Rodrigo, Ayaz, Fournier und Ruocco (2015) untersucht. Sie zeigten, dass kognitive Entscheidungsaufgaben mit einer tiefen Aufgabenanforderung bei weniger intelligenten Personen eine stärkere funktionelle Aktivität im frontalen Kortex hervorriefen als bei intelligenteren Personen. Der Unterschied in der funktionellen Hirnaktivität zwischen den Intelligenzgruppen verschwand bei Entscheidungen mit höheren Aufgabenanforderungen. Ein zweites Ziel der vorliegenden Studien (Witmer et al., 2018a, 2018b) war entsprechend die Prüfung, ob sich intelligenzbedingte Unterschiede der funktionellen Hirnaktivität mit fNIRS nachweisen lassen und wenn, ja, welche Richtung die Effekte aufweisen.

Die Fragestellungen zur Sensitivität, Spezifität und intelligenzbedingten Unterschieden der funktionellen Hirnaktivität wurden im Rahmen zweier Studien untersucht. Die Stichprobe der ersten Studie (Witmer et al., 2018a) bestand aus jungen Erwachsenen im Alter von 18 bis 24 Jahren. Ausgehend von den Ergebnissen dieser ersten Studie wurde in der zweiten Studie (Witmer et al., 2018b) überprüft, ob sich die Resultate der Erwachsenenstichprobe in einer Stichprobe mit Kindern im Alter von 11 bis 13 Jahren exakt replizieren, beziehungsweise ob sich die Befunde auf eine Kinderstichprobe generalisieren lassen. Dies ist sowohl aus wissenschaftlicher (Diener & Biswas-Diener, 2017; Maxwell, Lau & Howard, 2015; Open Science Collaboration, 2015) als auch aus anwenderbezogener Perspektive interessant, da fNIRS aufgrund der geringeren Belastung für die Versuchspersonen sehr gerne in Studien mit Kindern angewendet wird (Buss, Fox, Boas & Spencer, 2014; Moriguchi & Hiraki, 2013; Tsujimoto & Yamamoto, 2004).

Aus bisherigen Untersuchungen gibt es sowohl für Erwachsene (Neubauer, Fink & Schrausser, 2002; Neubauer, Grabner, Fink & Neuper, 2005; Tang et al., 2010) als auch Kinder (Schmithorst & Holland, 2006) Hinweise, dass der Zusammenhang zwischen Intelligenz und funktioneller Hirnaktivität auch durch das Geschlecht beeinflusst wird. So zeigten sich intelligenzbedingte funktionelle Hirnaktivitätsunterschiede in Abhängigkeit des Alters und Geschlechts bei Kindern (Schmithorst & Holland, 2006) als auch in Abhängigkeit des Aufgabentyps und Geschlechts bei Erwachsenen (Neubauer et al., 2005; Tang et al., 2010). Ob der Zusammenhang zwischen Intelligenz und funktioneller Hirnaktivität auch in den Daten der zwei vorliegenden Studien (Witmer et al., 2018a, 2018b) durch das Geschlecht beeinflusst wird, war Gegenstand einer zusätzlichen Analyse, die im Rahmen dieses Mantelpapiers durchgeführt wurde.

Im folgenden Abschnitt dieses Mantelpapiers wird die Funktionsweise der fNIRS vorgestellt. Anschliessend werden die aktuell wichtigsten methodischen Aspekte der fNIRS Forschung und deren Umsetzung in den zwei Studien erläutert. Hierzu werden einige bisher unveröffentlichte Ergebnisse präsentiert, die aufzeigen, inwiefern die methodische Vorgehensweise erfolgreich war. In einem weiteren Teil werden die in den zwei vorliegenden Studien (Witmer et al., 2018a, 2018b) untersuchten Fragestellungen, sowie die zusätzliche Fragestellung zu den Geschlechtsunterschieden genauer erläutert und die Ergebnisse der Erwachsenen- als auch der Kinderstichprobe diskutiert. Die direkte Gegenüberstellung der Resultate aus beiden Stichproben erleichtert deren Vergleich und Integration in die Gesamtdiskussion. Anschliessend werden die Befunde beider Studien und der zusätzlichen Analysen kurz zusammengefasst und die Anwendungsgrenzen aufgezeigt. Das Mantelpapier wird geschlossen mit einem Fazit und einem Ausblick für zukünftige fNIRS Forschung.

Die funktionelle Nah-Infrarot-Spektroskopie (fNIRS)

Die fNIRS misst Konzentrationsänderungen des Blutsauerstoffs im Gehirn während kognitiven, perzeptuellen und motorischen Prozessen. Die Ausführung solcher Prozesse erfordert Sauerstoff, welcher an Hämoglobin gebunden ist und über einen lokalen Anstieg des zerebralen Blutflusses bereitgestellt wird (Lindauer et al., 2010). Die Wechselwirkung zwischen Nervenzellaktivität, Metabolismus und gesteigertem Blutfluss ist als neurovaskuläre Kopplung bekannt. Obwohl dieses Phänomen seit vielen Jahren erforscht wird, sind die zellulären und molekularen Mechanismen dieser Wechselwirkung noch nicht vollständig geklärt (Keles, Barbour & Omurtag, 2016; Lindauer et al., 2010). Die Frage nach der auslösenden Struktur und dem genauen Mechanismus, der den Blutfluss und damit die Sauerstoffkonzentration bei funktioneller Hirnaktivität erhöht kann noch nicht eindeutig beantwortet werden (Chen, Kozberg,

Bouchard, Shaik & Hillman, 2014; Hillman, 2014; Lindauer et al., 2010; Magistretti & Allaman, 2015). Auch der exakte räumliche und zeitliche Zusammenhang dieser Wechselwirkung ist Gegenstand vieler Studien (Attwell & Iadecola, 2002; Devor, 2003; Huo, Smith & Drew, 2014; Leithner & Royl, 2014; Lindauer et al., 2010; Scott, 2015; Sirotin & Das, 2009). Für die Interpretation von fNIRS Daten ist der lineare Zusammenhang zwischen dem lokalen Blutfluss und der Nervenzellaktivität zentral (Nielsen & Lauritzen, 2001; Sheth et al., 2004). Eine Konzentrationsänderung des Blutsauerstoffs aufgrund einer kortikalen Aktivität (zum Beispiel durch die Verarbeitung eines Stimulus) wird als hämodynamische Antwortfunktion (HRF) sichtbar. Die HRF ist eine langsame Funktion, bei der die Konzentration des oxygenierten Hämoglobins (O_2Hb) kurz nach einer Stimulation ansteigt und gleichzeitig die Konzentration des deoxygenierten Hämoglobins (HHb) absinkt. Die Dauer und Höhe der Konzentrationsänderung ist von der Stimulationsdauer abhängig (Wüstenberg, Giesel & Strasburger, 2005). Bei einer längeren Stimulation von beispielsweise 15 Sekunden steigt das O_2Hb innert ungefähr 10 Sekunden an, bleibt anschliessend auf einem Plateau und kehrt innert ungefähr 15 Sekunden nach Beendigung der Stimulation auf das Ausgangsniveau zurück (Cohen, 1997; Friston, Frith, Turner & Frackowiak, 1995). Die Konzentrationsänderung des HHb ist etwa viermal kleiner als diejenige des O_2Hb (Wolf et al., 2002). Entsprechend der HRF, die eine funktionelle Hirnaktivität indiziert, sollte die Konzentrationsänderung von O_2Hb und HHb negativ korreliert sein (Cui, Bray & Reiss, 2010; Malonek & Grinvald, 1996; Tachtsidis & Scholkmann, 2016; Zimeo Morais et al., 2017). Cui et al. (2010) zeigten allerdings, dass Kopfbewegungen während der fNIRS Messung die negative Korrelation zwischen O_2Hb und HHb verringern, beziehungsweise sogar zu einer positiven Korrelation zwischen den zwei Signalen führen können. Die Höhe der negativen Korrelation zwischen O_2Hb und HHb gibt folglich auch Auskunft über die Qualität der gemessenen Daten.

Bei der fNIRS wird Licht im Bereich des Nah-Infrarot-Spektrums ins Gehirn gestrahlt. Das Nah-Infrarotlicht folgt einem bananenförmigen Pfad durch das Gewebe, wird gestreut und in Abhängigkeit der molekularen Eigenschaften eines Stoffes auf dem Lichtpfad absorbiert (Jöbsis, 1977). Da HHb Licht mit Wellenlängen unter 800 Nanometern und O_2Hb Licht mit Wellenlängen über 800 Nanometern besser absorbiert, wird bei der fNIRS Nah-Infrarotlicht zweier unterschiedlicher Wellenlängen in das Gehirn eingestrahlt, das jeweils für O_2Hb und HHb ein Absorptionsmaximum aufweist. Die wenige Zentimeter von der Lichtquelle entfernten Lichtdetektoren messen kontinuierlich die Intensität des Lichts. Daraus wird mit Hilfe des modifizierten Beer-Lambertschen Gesetzes (Delpy et al., 1988) die Konzentrationsänderung des O_2Hb und HHb berechnet. Je kürzer die Distanz zwischen Lichtquelle und Lichtdetektor ist,

desto geringer ist auch die Eindringtiefe des Lichts. So liegt die Eindringtiefe bei einem Standardabstand von 30 mm zwischen Lichtquelle und Lichtdetektor bei ungefähr 13 mm (Patil, Safaie, Moghaddam, Wallois & Grebe, 2011). Eine grössere Eindringtiefe kann über eine Verlängerung des Abstands zwischen Lichtquelle und Lichtdetektor, allerdings nur auf Kosten eines schlechteren Signal-Rausch-Verhältnisses erreicht werden (Calderon-Arnulphi, Alaraj & Slavin, 2009). Für kortikale Messungen hat sich eine Distanz von 30 mm zwischen Lichtquelle und Lichtdetektor etabliert (Brigadoi & Cooper, 2015). Bei dieser Distanz ergibt sich gemäss mehreren Forschungsgruppen (Boas, Dale & Franceschini, 2004; Strangman, Li & Zhang, 2013) ein optimales Verhältnis zwischen einer hinreichenden Eindringtiefe des Lichts bei ausreichend guter Signalqualität.

Ausschlaggebend für die Signalqualität und dafür, wie viel kortikales Gewebe gemessen wird, ist aber nicht nur der Abstand zwischen Lichtquelle und Lichtdetektor (Gunadi, Leung, Elwell & Tachtsidis, 2014; Patil et al., 2011) sondern auch die Dicke der extrazerebralen Schicht (Cui et al., 2011; Strangman, Zhang & Li, 2014). Diese setzt sich aus der Kopfhaut, dem Schädelknochen und der zerebrospinalen Flüssigkeit zusammen (Strangman et al., 2014). Die Dicke dieser Schicht ist über den gesamten Kopf betrachtet heterogen, wobei sie im frontalen Bereich am dünnsten ist (Beauchamp et al., 2011; Brigadoi & Cooper, 2015). Auch altersbedingt zeigen sich Unterschiede. So ist die extrazerebrale Schicht bei Kindern dünner und wird bis ins Erwachsenenalter dicker (Beauchamp et al., 2011). Die Kopfhaut und das Schädelgewebe sind stark vaskularisiert und Konzentrationsänderungen des Blutsauerstoffs dieser Schichten können durch die Herztätigkeit, die Atmung, Blutdruckveränderungen und Vasomotion verursacht werden (Franceschini et al., 2002; Julien, 2006; Obrig et al., 2000). Dieses durch die oberflächliche Durchblutung verursachte Störsignal ist oft mit der darunterliegenden funktionellen Aktivität des Kortex korreliert (Holper, Scholkmann & Wolf, 2014; Minati, Kress, Visani, Medford & Critchley, 2011; Takahashi et al., 2011). So kann es durch die kognitive Beanspruchung während der Bearbeitung einer Aufgabe zu einer Erhöhung der Herzfrequenz und des Blutdrucks kommen (Mandrick, Peysakhovich, Rémy, Lepron & Causse, 2016).

Um zu vermeiden, dass ein Signal aus der extrazerebralen Schicht als funktionelle Aktivität des Kortex interpretiert wird, empfehlen Saager und Berger (2005) die Verwendung von zusätzlichen kürzeren Messdistanzen zwischen Lichtquellen und Lichtdetektoren. Über diese kürzeren Distanzen wird ausschliesslich die Konzentrationsänderung der extrazerebralen Schicht gemessen. Das Signal der kurzen Kanäle kann anschliessend aus dem Signal der längeren Kanäle regressiert werden, um dadurch das Signal des Kortex zu isolieren (Saager & Berger, 2005).

Im Vergleich zu anderen bildgebenden Verfahren weist die fNIRS einige Vorteile auf. So ist sie nicht invasiv (Villringer & Chance, 1997), erzeugt keinen Lärm und das Signal unterliegt nur minimaler Beeinträchtigung durch leichte Bewegungen der Versuchspersonen (Brigadoi et al., 2014). Folglich ist das Verfahren für Versuchspersonen deutlich weniger belastend und kann deshalb bei Kindern (Anderson et al., 2014; Dresler et al., 2009; Lloyd-Fox et al., 2014; Marx et al., 2014; Perlman, Luna, Hein & Huppert, 2014) sowie Erwachsenen mit psychischen (Ehlis, Schneider, Dresler & Fallgatter, 2014; Marumo et al., 2014; Pu et al., 2012) oder kognitiven Beeinträchtigungen (Ferrari & Quaresima, 2012; Niu et al., 2013) sehr gut angewendet werden. Des Weiteren ist fNIRS kostengünstiger als fMRI und ermöglicht die Messung funktioneller Hirnaktivität während Aufgaben, die ein komplexes Antwortformat (zum Beispiel eine mündliche Antwort) (Dieler, Tupak & Fallgatter, 2012; Quaresima, Bisconti & Ferrari, 2012; Schecklmann, Ehlis, Plichta & Fallgatter, 2008) oder motorische Reaktionen (Ernst et al., 2013) erfordern. Moderne fNIRS Geräte sind klein, praktisch zu transportieren und weisen eine sehr gute zeitliche Auflösung auf (Boas et al., 2014).

METHODISCHE ASPEKTE DER fNIRS FORSCHUNG UND DEREN UMSETZUNG IN DEN ZWEI STUDIEN

In den folgenden Abschnitten werden einige der wichtigsten Herausforderungen der fNIRS Methode und die Vorgehensweise im Umgang mit diesen Herausforderungen in den beiden Studien aufgezeigt. Das Ziel war, die aktuellen methodischen Erkenntnisse mit den technischen und infrastrukturellen Möglichkeiten bestmöglich umzusetzen.

Extrazerebrale Konzentrationsänderungen

Das Problem, dass das fNIRS Signal sowohl das kortikale als auch das extrazerebrale Signal beinhaltet, wurde in den vorliegenden Studien (Witmer et al., 2018a, 2018b) über die Verwendung dreier unterschiedlicher Distanzen zwischen Lichtquelle und Lichtdetektor gelöst. Das für diese Studien verwendete NIRS-Gerät (FOIRE-3000, Shimadzu Corporation, Kyoto, Japan) ermöglichte eine Modifikation des Standardholders, so dass zehn Kanäle mit einem Abstand von 30 mm, sechs Kanäle mit einem Abstand von 42 mm und vier Kanäle mit einem Abstand von 15 mm gemessen werden konnten (siehe Abbildung 1). Da in beiden Studien nur die Kanäle 1-3 für weitere Analysen berücksichtigt wurden (siehe Abschnitt «Definition einer ‚Region of Interest' (ROI)»), werden in der Folge nur die Ergebnisse ebendieser Kanäle berichtet.

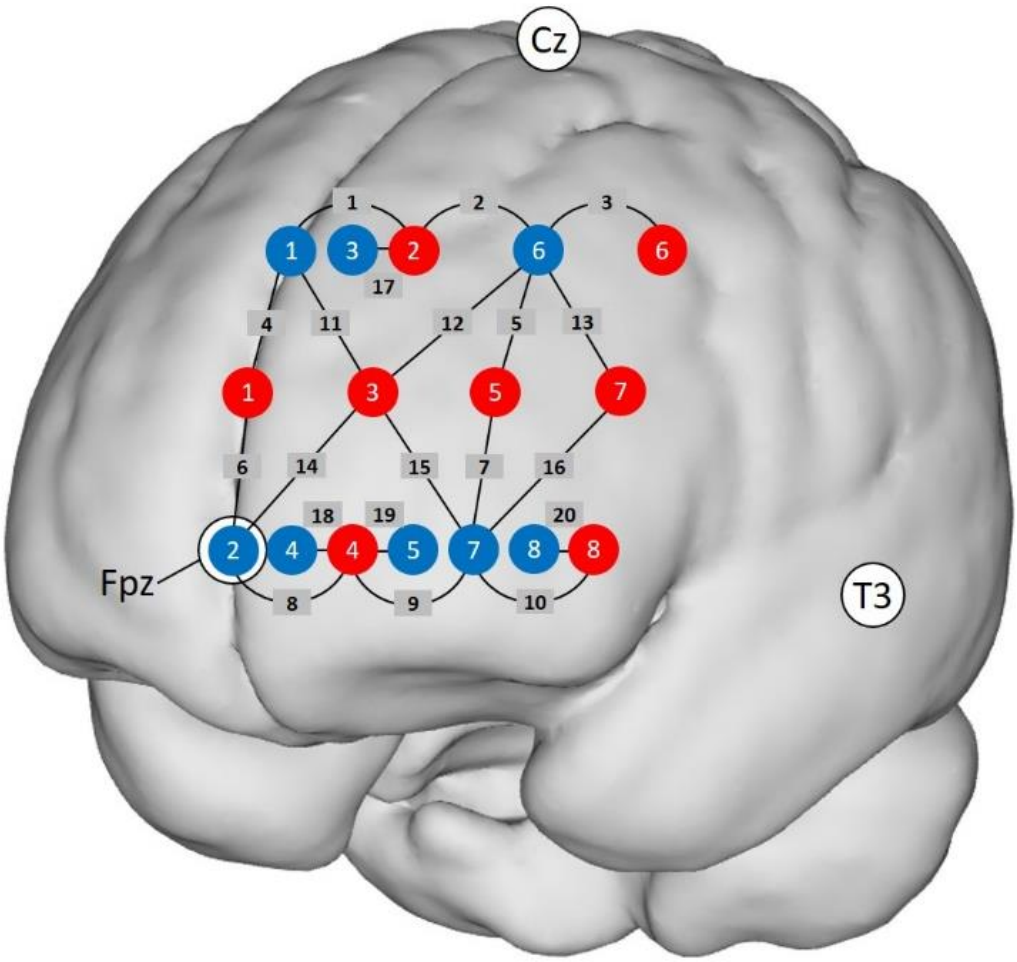

Abbildung 1. Die Positionen der 20 Kanäle auf ein Hirnmodell projiziert. Die roten Punkte stellen die Lichtquellen, die blauen Punkte die Lichtdetektoren dar. Die schwarzen Zahlen bezeichnen die Kanalnummern. Die Kanäle 1-10 wiesen einen Abstand von ~30 mm, die Kanäle 11-16 einen Abstand von ~42 mm und die Kanäle 17-20 einen Abstand von ~15 mm zwischen den Lichtquellen und Lichtdetektoren auf.

Entsprechend dem Kriterium von Gagnon et al. (2011) wurden auf Ebene des Individuums die Signale der längeren Kanäle 1 und 2 mit dem Signal des kurzen Kanals 17 und der längere Kanal 3 mit dem Mittelwert der Signale der kurzen Kanäle 17 und 20 regressiert, falls die Korrelation zwischen dem Signal des längeren und kürzeren Kanals einem Wert von $R^2 >$ .10 entsprach. In der Tabelle 1 ist der Stichprobenmittelwert des Determinationskoeffizienten (R^2) zwischen den jeweiligen langen und kurzen Kanälen für beide Aufgaben und Stichproben separat abgetragen.

Tabelle 1

Stichprobenmittelwerte des Determinationskoeffizienten (R^2) und Standardabweichung (SD) zwischen dem Signal der längeren (~30 mm) Kanäle 1, 2 und 3 und den kürzeren (~15 mm) Kanälen 17 und 20 für beide Aufgaben und beide Stichproben separat.

				Erwachsene		Kinder	
Aufgabe	Kanäle		Hämoglobin Oxygenierung	R^2	*SD*	R^2	*SD*
Arbeitsgedächtnis	1	17	O_2Hb	.71	.27	.63	.26
			HHb	.76	.24	.73	.20
	2	17	O_2Hb	.58	.25	.49	.29
			HHb	.66	.29	.60	.30
	3	17, 20	O_2Hb	.27	.23	.33	.25
			HHb	.16	.19	.16	.17
Zeitdauerdiskrimination	1	17	O_2Hb	.69	.25	.56	.29
			HHb	.71	.24	.70	.26
	2	17	O_2Hb	.52	.28	.45	.32
			HHb	.61	.29	.57	.27
	3	17, 20	O_2Hb	.29	.27	.19	.20
			HHb	.18	.22	.17	.19

Die Werte zeigen einen deutlichen Zusammenhang zwischen dem kortikalen und extrazerebralen Signal. Es fällt allerdings auf, dass sich der Zusammenhang in Abhängigkeit des Abstands zwischen dem kurzen und längeren Kanal veränderte. Der kürzere Abstand zwischen Kanal 1 und 17 führte zu höheren Korrelationen als der längere Abstand zwischen Kanal 2 und 17. Entsprechend dem Kriterium von $R^2 > .10$ wurden in der Erwachsenenstichprobe 95.9% der Daten des Kanals 1, 92.4% der Daten des Kanals 2 und noch 57.0% der Daten des Kanals 3 durch die Regression mit dem kurzen Kanal korrigiert. In der Kinderstichprobe waren die entsprechenden Werte 89.9%, 83.3% und 52.4%. Sowohl die Stichprobenmittelwerte des Determinationskoeffizienten (R^2) als auch der prozentuale Anteil korrigierter Daten der vorliegenden Studien (Witmer et al., 2018a, 2018b) entsprechen den Ergebnissen von Gagnon et al. (2012), die zeigten, dass der Zusammenhang zwischen dem kortikalen und dem extrazerebralen Signal umso geringer wird, je grösser der Abstand zwischen dem jeweiligen kurzen und längeren Kanal ist. Aufgrund der Tatsache, dass die extrazerebrale Durchblutung lokal verschieden und heterogen über den Kopf verteilt ist, empfehlen Gagnon et al. (2012) einen idealen Abstand zwischen dem kurzen und längeren Kanal von maximal 15 mm. Ab einem Abstand von 20 mm würden die Daten durch die Regression mit den kurzen Kanälen kaum mehr verbessert. Bei der in den vorliegenden Studien (Witmer et al., 2018a, 2018b) verwendeten Holderkonfiguration war ein so kurzer Abstand des kürzeren zum längeren Kanal nur bei Kanal 1 möglich (7.5 mm).

Der Abstand des kurzen Kanals zu Kanal 2 betrug 22.5 mm und zu Kanal 3 mehr als 50 mm. Trotz dieser grösseren Abstände in unseren Studien, wurde dennoch ein substanzieller Anteil des Signals der längeren Kanäle durch die kürzeren Kanäle korrigiert.

Bewegungsartefakte

Obwohl fNIRS im Vergleich zu fMRI eine deutlich grössere Toleranz gegenüber Bewegungsartefakten aufweist, können Bewegungen der Versuchspersonen (beispielsweise durch Husten, Kratzen oder motorische Unruhe) das Signal-Rausch-Verhältnis und entsprechend die Datenqualität deutlich reduzieren (Scholkmann, Spichtig, Muehlemann & Wolf, 2010; Yücel, Selb, Boas, Cash & Cooper, 2014). Bewegungsartefakte stellen folglich eine Störvariable dar, die aus dem Signal entfernt werden sollte (Scholkmann, Metz & Wolf, 2014). Eine valide aber aufwändige Möglichkeit damit umzugehen, ist die Korrektur der Daten gemäss dem Vorgehen von Scholkmann et al. (2010). Sie empfehlen eine visuelle Identifikation und manuelle Selektion von Parametern zur Korrektur der Bewegungsartefakte, da das menschliche Auge am besten zwischen Signalen mit und ohne Artefakten unterscheiden könne. Dies wurde in den vorliegenden Studien (Witmer et al., 2018a, 2018b) entsprechend umgesetzt. Die subjektive Wahrnehmung der Versuchsleiter, dass sich die Kinder während der fNIRS Messung stärker bewegten als die Erwachsenen wurde durch die Analyse des prozentualen Anteils korrigierter Daten bestätigt. So wurden in der Erwachsenenstichprobe in den Kanälen 1-3 weniger Bewegungsartefakte korrigiert (Mittelwert ± Standardabweichung: 0.4 ± 0.5 % (Arbeitsgedächtnisaufgabe); 0.3 ± 0.5 % (Zeitdauerdiskriminationsaufgabe)) als bei den Kindern (Mittelwert ± Standardabweichung: 2.3 ± 5.9 % (Arbeitsgedächtnisaufgabe); 1.6 ± 2.3 % (Zeitdauerdiskriminationsaufgabe)). Die Kinder wiesen über beide Aufgaben hinweg signifikant mehr Bewegungsartefakte auf (Median = 0.67) als die Erwachsenen (Median = 0.27); Mann-Whitney-U-Test: $U = 362.0$, $p < .001$.

Unterschiede in der Kopfgrösse und -anatomie

Eine weitere Herausforderung, die sich bei fNIRS Messungen im Vergleich zu anderen bildgebenden Verfahren stellt, ist der unflexible Holder mit den fixierten Abständen zwischen den Lichtquellen und Lichtdetektoren. Obwohl die Dicke der extrazerebralen Schicht zwischen Versuchspersonen variieren kann, ist sie dennoch innerhalb derselben Altersgruppe und desselben Bereiches des Kopfs relativ homogen (Beauchamp et al., 2011; Brigadoi & Cooper, 2015). Fixierte Abstände zwischen Lichtquellen und Lichtdetektoren stellen entsprechend sicher, dass das Signal-Rausch-Verhältnis der Daten und die Eindringtiefe des Lichts zwischen den Ver-

suchspersonen konstant gehalten werden. Grössere anatomische Unterschiede könnten allerdings dazu führen, dass nicht bei allen Versuchspersonen durch denselben Kanal dasselbe Hirnareal erfasst wird. Dies würde die Vergleichbarkeit der Daten stark erschweren. Aus diesem Grund wurden in den vorliegenden Studien (Witmer et al., 2018a, 2018b) analog zum Vorgehen bei Singh, Okamoto, Dan, Jurcak und Dan (2005) die Kanalpositionen mittels eines 3D Digitalisierers (FASTRAK, Polhemus, Colchester, VT, USA) bei jeder einzelnen Versuchsperson erfasst. Die Abweichung der Kanalpositionen innerhalb beider Stichproben sowie zwischen Kindern und Erwachsenen war nur minimal. Entsprechend wurde in beiden Stichproben mit den Kanälen 1-3 das Brodmann Areal 8 gemessen. Nur ein Kind wurde aufgrund einer Abweichung der Koordinatenpunkte von mehr als zwei Standardabweichungen vom Mittelwert der Stichprobe aus den weiteren Analysen ausgeschlossen. Die präzise Lokalisation der gemessenen Hirnareale ermöglicht nicht nur die Überprüfung der Übereinstimmung innerhalb derselben Stichprobe, sondern auch den wichtigen Vergleich der Ergebnisse einer Studie mit den Ergebnissen anderer fNIRS oder fMRI Studien.

Definition einer ‚Region of Interest' (ROI)

Für die Definition einer ROI wurde in der Erwachsenenstichprobe ein datengeleiteter Ansatz gewählt (Plichta et al., 2006). Zuerst wurde für jeden Kanal, beide Aufgaben (Arbeitsgedächtnis- und Zeitdauerdiskrimination) und beide Bedingungen (aktive Kontroll- und Experimentalbedingung) die Korrelation zwischen O_2Hb und HHb ermittelt. Für die weiteren Analysen wurden schliesslich nur diejenigen Kanäle ausgewählt, die eine signifikant negative Korrelation zwischen O_2Hb und HHb, verursacht durch einen Anstieg in O_2Hb bei gleichzeitigem Absinken des HHb aufwiesen. Daran ist sowohl eine funktionelle Hirnaktivität (Devor, 2003; Malonek & Grinvald, 1996; Mayhew et al., 1999; Sheth et al., 2004; Tang, Avison & Gore, 2009) als auch eine gute Signalqualität (Cui et al., 2010) erkennbar. In der Erwachsenenstichprobe erfüllten die Kanäle 1, 2 und 3 dieses Kriterium. Die Kanäle 1 und 2 massen kortikales Gewebe des linken superioren, der Kanal 3 des linken mittleren frontalen Gyrus. Alle drei Kanäle repräsentierten das Brodmann Areal 8. Um die Ergebnisse der Erwachsenenstichprobe möglichst exakt auch bezüglich des gemessenen Hirnareals in der Kinderstichprobe zu replizieren, wurden in der Kinderstichprobe ebenfalls die Kanäle 1-3 analysiert. Auch hier zeigte sich eine signifikant negative Korrelation zwischen O_2Hb und HHb entsprechend dem Muster der funktionellen Hirnaktivität (Anstieg im O_2Hb bei gleichzeitigem Absinken des HHb). Dass in beiden Stichproben während der Bearbeitung der visuell-räumlichen Arbeitsgedächtnisaufgabe eine funktionelle Hirnaktivität im Brodmann Areal 8 gemessen wurde, passt zu den Befunden bisheriger Studien, die diesem Areal eine wichtige Funktion bei der Verarbeitung von

visuell-räumlichen Arbeitsgedächtnisaufgaben zuschreiben. Boisgueheneuc et al. (2006) untersuchten Patienten mit einer Läsion im Brodmann Areal 8, Patienten mit Läsionen in anderen frontalen Hirnarealen und gesunde Kontrollpersonen während der Bearbeitung von n-Back Aufgaben unterschiedlicher Modalitäten. Insbesondere in der 3-Back Bedingung der visuell-räumlichen Modalität wiesen die Patienten mit der Läsion im Brodmann Areal 8 signifikant schlechtere Leistungen auf als die anderen Läsionspatienten und die gesunden Kontrollpersonen. Die funktionelle Hirnaktivität wird aber nicht nur von der Aufgabenmodalität, sondern auch von den durch die Aufgabe beanspruchten Arbeitsgedächtnisprozessen (zum Beispiel Enkodierung, Speicherung und Abruf von Informationen) beeinflusst (Rottschy et al., 2012). So unterscheidet sich das funktionelle Hirnaktivitätsmuster in Abhängigkeit davon, ob eine Aufgabe das Wiedererkennen, die Lokalisation, die Identifikation oder die Reproduktion von Stimuli erfordert (Rottschy et al., 2012). Die in den vorliegenden Studien (Witmer et al., 2018a, 2018b) verwendete Arbeitsgedächtnisaufgabe beinhaltete die Speicherung der Lokalisation und anschliessende Reproduktion von Stimuli. Entsprechend der Meta-Analyse von Rottschy et al. (2012) sind genau diese Prozesse mit einer erhöhten funktionellen Hirnaktivität im posterioren superioren frontalen Gyrus (Brodmann Areal 8) assoziiert. Folglich passt die in beiden Stichproben gefundenen funktionelle Hirnaktivität im Brodmann Areal 8 sowohl zur Modalität der verwendeten Arbeitsgedächtnisaufgabe als auch zu den durch diese Aufgabe beanspruchten Arbeitsgedächtnisprozessen.

Task Design

Die Aufgaben während der fNIRS Messung wurden im Block Design präsentiert. Jeder einzelne aktive Kontroll- und Experimentalblock dauerte 40 Sekunden. Dadurch konnte sichergestellt werden, dass auch diejenigen Versuchspersonen mit einer sehr langen Arbeitsgedächtnisspanne in der Experimentalbedingung mindestens zwei Aufgaben pro Block bearbeiten konnten. In der Erwachsenenstichprobe wurden in der aktiven Kontrollbedingung im Mittel pro Block (Mittelwert ± Standardabweichung) 3.47 ± 0.47 und in der Experimentalbedingung 3.18 ± 0.44 Aufgaben bearbeitet. In der Kinderstichprobe wurden in der aktiven Kontrollbedingung 4.29 ± 0.71 und in der Experimentalbedingung 4.13 ± 0.67 Aufgaben bearbeitet. Entsprechend der 40 Sekunden andauernden Beanspruchung während der Experimentalbedingung war anzunehmen, dass die HRF während den ersten 8 Sekunden der Bedingung ansteigt, anschliessend 32 Sekunden auf einem konstanten Konzentrationsniveau verbleibt (Wüstenberg et al., 2005) und schliesslich innert ungefähr 10-23 Sekunden nach Abschluss der Bedingung auf das Ausgangsniveau zurückkehrt (Boynton, Engel, Glover, & Heeger, 1996; Buckner et al., 1996; Friston et al., 1995; Cohen, 1997). Um eine optimale Vergleichbarkeit der Experimental- mit

der aktiven Kontrollbedingung zu erreichen, wurde die Dauer der aktiven Kontrollbedingung ebenfalls auf 40 Sekunden festgesetzt. Die Darbietung der vier aktiven Kontroll- und vier Experimentalblöcke erfolgte jeweils abwechslungsweise. Zwischen jeder aktiven Bedingung wurde ein Ruheblock mit einer variablen Dauer zwischen 25 und 45 Sekunden präsentiert. Während dieses Ruheblocks sollten sich die Versuchspersonen mit geöffneten Augen entspannen. Die minimale Dauer der Ruheblöcke von 25 Sekunden stellte sicher, dass die HRF ausreichend Zeit hatte, nach der Beanspruchung durch eine der Bedingungen auf das Ausgangsniveau zurückzukehren. Die Dauer der Ruheblöcke wurde variiert, da es aus der Literatur Hinweise gibt, dass sich die sogenannten Mayer Wellen in einem Block Design mit der Stimulationsdauer synchronisieren können (Leff et al., 2011). Mayer Wellen sind spontane hämodynamische Oszillationen im niedrigen Frequenzbereich von 0.1 Hz (Julien, 2006) und liegen innerhalb des Frequenzspektrums des fNIRS-Signals, weshalb es kaum möglich ist, diese ohne Beeinträchtigung des kortikalen fNIRS-Signals herauszufiltern (Yücel et al., 2016). Da im Block Design (im Vergleich zum ereigniskorrelierten Design) die funktionelle Hirnaktivität während falsch gelösten Aufgaben nicht aus dem Gesamtsignal herausgerechnet werden kann (Petersen & Dubis, 2012), ist die Aufzeichnung der Antworten während des Experiments und die anschliessende Prüfung des prozentualen Anteils richtig bearbeiteter Aufgaben pro Versuchsperson besonders wichtig. In beiden Studien wurden pro Versuchsperson aktive Kontrollblöcke mit weniger als 80% richtigen Antworten und Experimentalblöcke mit weniger als 50% richtigen Antworten aus den weiteren Analysen ausgeschlossen. Anschliessend wurde überprüft, ob pro Versuchsperson noch mindestens drei aktive Kontroll- und drei Experimentalblöcke für die weiteren Analysen verwendet werden konnten. Vier Kinder mussten aufgrund dieser Kriterien aus den weiteren Analysen ausgeschlossen werden. Bei vier Erwachsenen (9.3% der finalen Stichprobe) konnten nur jeweils drei der vier Kontrollblöcke ausgewertet werden (hingegen alle vier Experimentalblöcke).

Subjektive Aufgabenschwierigkeit

Ein zentrales Ziel der vorliegenden Studien (Witmer et al., 2018a, 2018b) war die Messung der funktionellen Hirnaktivität aufgrund der Beanspruchung ganz spezifischer visuell-räumlicher Arbeitsgedächtnisprozesse. Interindividuelle Differenzen der subjektiven Aufgabenschwierigkeit können Unterschiede in der funktionellen Hirnaktivität hervorrufen (Basten, Hilger & Fiebach, 2015; Parks et al., 1988). Dies bedeutet, dass eine funktionelle Hirnaktivität, bei fehlender oder unzureichender Kontrolle der subjektiven Aufgabenschwierigkeit, nicht eindeutig auf spezifische Prozesse zurückgeführt werden kann. Um dies zu verhindern, wurde in beiden vorliegenden Studien (Witmer et al., 2018a, 2018b) jeweils vor dem fNIRS Experiment

eine separate Testsitzung durchgeführt, bei der ein adaptives Verfahren (Kaernbach, 1991) eingesetzt wurde, mit dem Ziel, diejenige Zeitdauer (bei der Zeitdauerdiskriminationsaufgabe) beziehungsweise diejenige Arbeitsgedächtnisspanne (bei der visuell-räumlichen Arbeitsgedächtnisaufgabe) zu ermitteln, bei der mit einer Wahrscheinlichkeit von 75% die richtige Antwort gegeben wird. Dieses Vorgehen stellte sicher, dass die Aufgaben während der fNIRS Messung für alle Versuchspersonen subjektiv vergleichbar schwierig waren. Dies wiederum ermöglichte den Vergleich der funktionellen Hirnaktivität, die (1) durch zwei unterschiedliche Aufgaben bei derselben Versuchsperson und (2) während derselben Aufgabe zwischen verschiedenen Versuchspersonen hervorgerufen wurde. In der Tabelle 2 sind die Arbeitsgedächtnisspannen und Zeitdauerdiskriminationsschwellen sowie die prozentualen Anteile richtiger Antworten während der fNIRS Messung für beide Bedingungen (aktive Kontroll- und Experimentalbedingung) in beiden Stichproben ersichtlich.

Stichproben

Für die Erwachsenenstichprobe wurden 295 Männer und Frauen im Alter zwischen 18 und 24 Jahren mit dem CFT 20-R (Weiß, 2006) an Berufsschulen und an der Universität rekrutiert und getestet. Aus dieser Gruppe wurden diejenigen Personen selektioniert, welche einen IQ von ≥ 130 Punkten (IQ↑: 130-145) oder eine IQ von ≤ 112 Punkten (IQ↓: 90-112) aufwiesen. Um zwischen den Gruppen eine Überlappung im 95% Konfidenzintervall zu verhindern, war ein Gruppenunterschied von mindestens 16 IQ Punkten notwendig. In die Studie eingeschlossen wurden ausschliesslich rechtshändige Personen die ein unbeeinträchtigtes Hörvermögen und gutes Sehvermögen (mit oder ohne Sehhilfe) angegeben haben. Weitere Ausschlusskriterien waren Rauchen, übermässiger Alkoholkonsum, aktuelle oder vergangene neurologische oder psychische Erkrankungen sowie die Einnahme von Drogen oder Psychopharmaka. In die Datenanalyse der ersten Studie wurden 22 Versuchspersonen für die IQ↑ Gruppe (11 Frauen) und 21 Versuchspersonen für die IQ↓ Gruppe (11 Frauen) eingeschlossen.

Für die Kinderstichprobe wurden über öffentliche Schulen 250 Kinder im Alter zwischen 11 und 13 Jahren rekrutiert und ebenfalls mit dem CFT 20-R (Weiß, 2006) getestet. In die IQ↑ Gruppe wurden Kinder mit einem IQ ≥ 115 Punkten (115-141) in die IQ↓ Gruppe Kinder mit einem IQ ≤ 96 Punkten eingeschlossen. Die IQ↑ Gruppe bestand aus 24 Kindern (12 Mädchen), die IQ↓ aus 18 Kindern (10 Mädchen). Die genauen Angaben zur Alters- und IQ-Verteilung innerhalb der Kinder- und Erwachsenenstichprobe sind in Tabelle 2 zu sehen.

Tabelle 2

Mittelwerte (M) und Standardabweichungen (SD) des Alters, des IQs sowie der Arbeitsgedächtnisspanne und Zeitdauerdiskriminationsschwelle und die prozentualen Anteile richtiger Antworten in den beiden Aufgaben während des fNIRS Experiments. Die Werte sind für die gesamte Erwachsenen- und Kinderstichprobe (Total) als auch für die jeweiligen Intelligenzgruppen (IQ↑ und IQ↓) separat aufgeführt. T-Tests und Effektgrössen (Cohen's d) zum Vergleich der beiden Gruppen.

	Erwachsene (*N* = 43)									Kinder (*N* = 42 / 37)								
	Total		IQ↑ (*n* = 22)		IQ↓ (*n* = 21)					Total		IQ↑ (*n* = 24)		IQ↓ (*n* = 18)				
	M	*SD*	*M*	*SD*	*M*	*SD*	*t*(41)	*p*	*d*	*M*	*SD*	*M*	*SD*	*M*	*SD*	*t*(40)	*p*	*d*
Alter	21.3	1.88	20.8	2.08	21.9	1.53	-1.86	.070	-0.57	11.7	0.60	11.8	0.59	11.6	0.61	0.97	.340	0.59
IQ (CFT 20-R)	119.7	17.69	135.7	4.86	102.8	7.10	17.82	.001	5.41	108.0	18.17	122.2	7.88	89.1	7.17	13.97	.001	4.39
Arbeitsgedächtnisaufgabe																		
Spanne	5.9	0.97	6.4	0.91	5.4	0.74	4.06	.001	1.24	4.0	0.99	4.3	0.94	3.8	1.00	1.56	.126	0.49
% richtige Antworten																		
Kontrollbedingung	99.0	2.38	98.9	2.56	99.1	2.23	-0.23	.823	-0.08	99.5	1.28	100.0	0.00	98.9	1.79	3.07	.004	0.89
Experimentalbedingung	88.6	7.18	88.4	7.23	88.9	7.28	-0.25	.804	-0.07	92.1	6.13	92.6	6.17	91.4	6.19	0.62	.541	0.19
												IQ↑ (*n* = 20)		IQ↓ (*n* = 17)				
Zeitdauerdiskriminationsaufgabe												*M*	*SD*	*M*	*SD*	*t (35)*		
Schwelle (in ms)	28.7	10.61	27.3	10.12	30.2	11.15	-0.91	.369	-0.28	38.7	15.59	34.7	9.76	43.3	19.78	-1.718	.095	-0.55
% richtige Antworten																		
Kontrollbedingung	94.6	2.85	94.7	2.91	94.5	2.86	0.63	.530	0.09	92.7	3.61	92.8	3.19	92.5	4.15	0.21	.834	0.07
Experimentalbedingung	78.0	9.84	77.1	9.85	79.0	9.98	-0.28	.783	-0.19	76.3	10.08	77.1	8.75	75.5	11.68	0.46	.647	0.15

FRAGESTELLUNGEN

Ist fNIRS ausreichend sensitiv, um spezifische, visuell-räumliche Arbeitsgedächtnisprozesse zu messen?

Das in beiden vorliegenden Studien (Witmer et al., 2018a, 2018b) umgesetzte Vorgehen zur Überprüfung der Sensitivität von fNIRS, basierend auf einer Variation im Aufgabendesign unter Berücksichtigung der subjektiven Aufgabenschwierigkeit wurde bisher in keiner anderen fNIRS Studie durchgeführt. Aus früheren fNIRS Studien ist bekannt, dass eine zunehmende Beanspruchung während Arbeitsgedächtnisaufgaben mit einer stärkeren funktionellen Hirnaktivität einhergeht (Ayaz et al., 2012; Causse et al., 2017; Fishburn et al., 2014; Herff et al., 2014; Li et al., 2010; Molteni et al., 2012). Aus diesem Befund kann geschlossen werden, dass fNIRS ausreichend sensitiv ist, um funktionelle Hirnaktivitätsunterschiede abzubilden, die während der Bearbeitung von einfacheren und schwierigeren Arbeitsgedächtnisaufgaben auftreten. Aufbauend auf dieser Erkenntnis wurde in den vorliegenden Studien (Witmer et al., 2018a, 2018b) überprüft, ob fNIRS auch ausreichend sensitiv ist, um einen Unterschied zwischen der funktionellen Hirnaktivität, die aufgrund von aufgabenspezifischen Prozessen zustande kommt und funktioneller Hirnaktivität aufgrund von allgemeineren, wenig aufgabenspezifischen Prozessen zu messen. Dazu wurde die funktionelle Hirnaktivität während der aktiven Kontrollbedingung mit derjenigen während der Experimentalbedingung verglichen.

Sowohl in der Erwachsenen- als auch in der Kinderstichprobe wurde die Interaktion zwischen Hämoglobin Oxygenierung (O_2Hb und HHb) und Bedingung (aktive Kontroll- und Experimentalbedingung) signifikant. In beiden Stichproben zeigte sich während der Bearbeitung der Experimentalbedingung das typische Muster der funktionellen Hirnaktivität mit einer Zunahme der O_2Hb-Konzentration bei gleichzeitiger Abnahme der HHb-Konzentration. Während der aktiven Kontrollbedingung wurde bei den Erwachsenen keine funktionelle Hirnaktivität erkennbar, bei den Kindern hingegen schon. Diese war jedoch deutlich schwächer ausgeprägt als in der experimentellen Bedingung (siehe Abbildung 2).

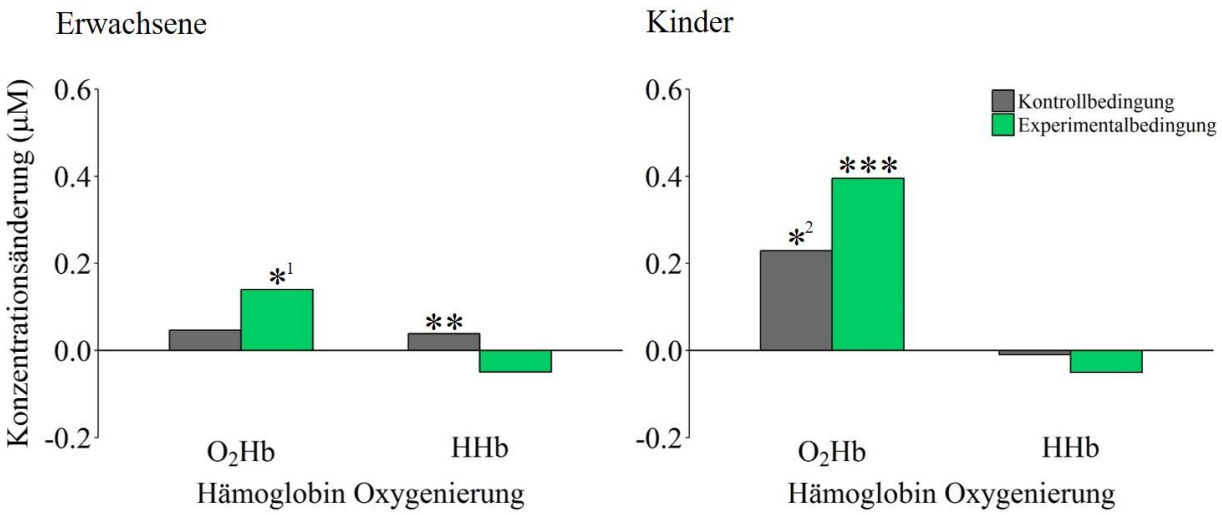

Abbildung 2. Unterschiede der Konzentrationsänderungen bei oxygeniertem (O_2Hb) und deoxygeniertem (HHb) Hämoglobin als Funktion der Bedingung während der Arbeitsgedächtnisaufgabe. Innerhalb der Erwachsenen- als auch der Kinderstichprobe zeigte sich ein signifikanter Unterschied zwischen O_2Hb und HHb in der Experimentalbedingung. In der Kinderstichprobe wurde dieser Unterschied auch in der aktiven Kontrollbedingung signifikant. In der Erwachsenenstichprobe wurde zusätzlich der Unterschied zwischen der aktiven Kontroll- und Experimentalbedingung im HHb signifikant. *[1]: Signifikant verschieden zur HHb-Konzentrationsänderung in der Experimentalbedingung ($p < .05$); *[2]: Signifikant verschieden zur HHb-Konzentrationsänderung in der aktiven Kontrollbedingung ($p < .05$); **: Signifikant verschieden zur HHb-Konzentrationsänderung in der Experimentalbedingung ($p < .01$); ***: Signifikant verschieden zur HHb-Konzentrationsänderung in der Experimentalbedingung ($p < .001$).

Diese Ergebnisse zeigen, dass fNIRS ausreichend sensitiv ist, um funktionelle Hirnaktivitätsunterschiede abzubilden, die während der Bearbeitung einer subjektiv einfachen Experimentalbedingung und einer aktiven Kontrollbedingung in einer visuell-räumlichen Arbeitsgedächtnisaufgabe zustande kamen. Sie klären jedoch noch nicht vollständig, ob die funktionelle Hirnaktivität durch spezifische arbeitsgedächtnisbezogene Prozesse oder durch eine generell höhere Aufgabenanforderung in der Experimentalbedingung im Vergleich zur aktiven Kontrollbedingung zustande kam. Um diese Frage abschliessend zu beantworten, war zusätzlich die im folgenden Abschnitt beschriebene Vorgehensweise notwendig.

Werden die im fNIRS gemessenen funktionellen Hirnaktivitätsunterschiede tatsächlich durch spezifische, visuell-räumliche Arbeitsgedächtnisprozesse oder lediglich durch höhere Aufgabenanforderungen in der Experimentalbedingung verursacht?

Um dies zu überprüfen, wurde eine visuelle Zeitdauerdiskriminationsaufgabe als Vergleichsaufgabe implementiert, die funktionell von Arbeitsgedächtnisprozessen unabhängig ist. Zeitdauerdiskriminationsaufgaben, die eine Diskrimination im Bereich von Millisekunden erfordern, beanspruchen vorwiegend sensorisch-perzeptuelle und kaum kognitive Prozesse

(Buonomano, 2014; Koch, Oliveri & Caltagirone, 2009; Michon, 1985; Münsterberg, 1889; Rammsayer, 2012; Rammsayer & Lima, 1991; Rammsayer & Ulrich, 2011). Auf Nervenzellebene zeigt sich dies durch eine erhöhte funktionelle Aktivität in subkortikalen Hirnarealen wie den Basalganglien und dem Kleinhirn bei nur geringfügiger oder keiner funktionellen Aktivität in kortikalen Hirnaralen (Wiener, Turkeltaub & Coslett, 2010). Um die funktionelle Hirnaktivität, die während der Arbeitsgedächtnisaufgabe beziehungsweise während der Zeitdauerdiskriminationsaufgabe auftrat vergleichen zu können, wurde analog zur Arbeitsgedächtnisaufgabe auch in der Zeitdauerdiskriminationsaufgabe eine aktive Kontroll- und eine Experimentalbedingung durchgeführt. Über das adaptive Verfahren wurde sichergestellt, dass auch die Stimuli der Zeitdauerdiskriminationsaufgabe während der fNIRS Messung für alle Versuchspersonen eine vergleichbare subjektive Aufgabenschwierigkeit aufwiesen.

Die Prozentwerte der richtig gelösten Antworten beider Aufgaben zeigten, dass die Zeitdauerdiskriminationsaufgabe in beiden Stichproben etwas schlechter gelöst wurde als die Arbeitsgedächtnisaufgabe (siehe Tabelle 2). Dies könnte bedeuten, dass die Aufgaben der visuellen Zeitdauerdiskriminationsaufgabe von den Versuchspersonen als subjektiv schwieriger erlebt wurden als diejenige der Arbeitsgedächtnisaufgabe. Weder in der Erwachsenen- noch in der Kinderstichprobe wurde die Interaktion zwischen Hämoglobin Oxygenierung (O_2Hb und HHb) und Bedingung (aktive Kontroll- und Experimentalbedingung) signifikant (siehe Abbildung 3).

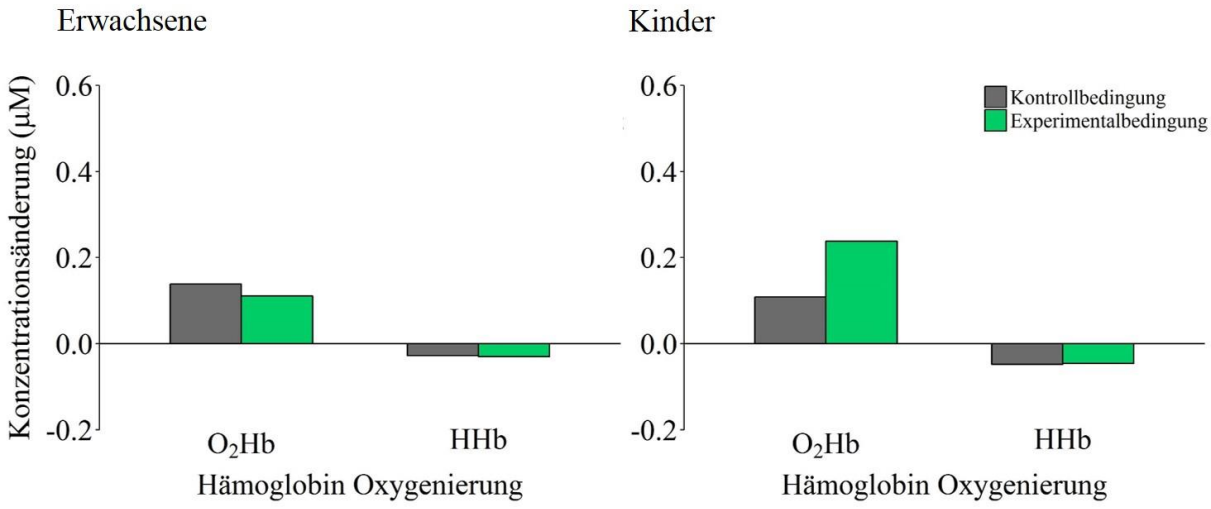

Abbildung 3. Unterschiede der Konzentrationsänderungen bei oxygeniertem (O_2Hb) und deoxygeniertem (HHb) Hämoglobin als Funktion der Bedingung während der Zeitdauerdiskriminationsaufgabe. Innerhalb der Erwachsenen- als auch der Kinderstichprobe zeigte weder ein signifikanter Unterschied zwischen O_2Hb und HHb innerhalb der jeweiligen Bedingung noch ein signifikanter Unterschied zwischen der aktiven Kontroll- und Experimentalbedingung innerhalb von O_2Hb und HHb.

Aufgrund der Ergebnisse zur Sensitivität und Spezifität lässt sich nun folgern, dass die funktionelle Hirnaktivität, die während der Bearbeitung der Experimentalbedingung bei der Arbeitsgedächtnisaufgabe auftrat tatsächlich auf arbeitsgedächtnisspezifische Prozesse und nicht auf einen unspezifischen und aufgabenunabhängigen Anstieg der Aufgabenanforderung zurückzuführen ist. Entsprechend ist auch die im Vergleich zur Arbeitsgedächtnisaufgabe etwas höhere subjektive Aufgabenschwierigkeit in der Zeitdauerdiskriminationsaufgabe unproblematisch. Letztere hätte das Auftreten eines generellen Effekts durch höhere Aufgabenanforderungen in der Zeitdauerdiskriminationsaufgabe gegenüber der Arbeitsgedächtnisaufgabe begünstigt.

Die Ergebnisse beider Studien sind in Übereinstimmung mit den fNIRS Studien, die während schwierigeren Arbeitsgedächtnisaufgaben eine stärkere funktionelle Hirnaktivität gefunden haben (Ayaz et al., 2012; Causse et al., 2017; Fishburn et al., 2014; Herff et al., 2014; Li et al., 2010; Molteni et al., 2012). Allerdings konnte erst durch das adaptive Vorgehen und die damit verbundene Vergleichbarkeit der subjektiven Aufgabenschwierigkeit zwischen den Versuchspersonen sowie der Implementierung einer Vergleichsaufgabe bestätigt werden, dass der Anstieg in der funktionellen Hirnaktivität aufgrund einer Beanspruchung spezifischer visuell-räumlicher Arbeitsgedächtnisprozesse zustande kommt. Folglich ist fNIRS hinreichend sensitiv um spezifische visuell-räumliche Arbeitsgedächtnisprozesse abzubilden.

Wird die funktionelle Hirnaktivität durch Intelligenzunterschiede moduliert?

Gemäss zahlreicher Studien unterscheidet sich das Gehirn von Personen unterschiedlicher Intelligenz sowohl auf struktureller (Gignac, Vernon & Wickett, 2003; Haier, 2011; McDaniel, 2005) als auch funktioneller Ebene (Park & Friston, 2013). Auf der funktionellen Ebene zeigte sich, dass Personen mit höherer Intelligenz während der Bearbeitung kognitiver Aufgaben weniger funktionelle Hirnaktivität aufweisen als Personen niedrigerer Intelligenz (Haier et al., 1988; Neubauer & Fink, 2009; Rypma, Berger & D'Esposito, 2002; Rypma, D'Esposito, D'Amato & D'Esposito, 1999). Denselben Befund bestätigten Schmithorst und Holland (2006) bei Knaben im Alter zwischen 13 und 18 Jahren. Diese intelligenzbedingten Hirnaktivitätsunterschiede konnten insbesondere in frontalen Hirnarealen (Haier et al., 1988; Neubauer & Fink, 2009; Schmithorst & Holland, 2006) und in Abhängigkeit der Beanspruchung durch die Aufgaben (Di Domenico et al., 2015; Larson, Haier, LaCasse & Hazen, 1995; Neubauer & Fink, 2009) nachgewiesen werden. Gemäss einer Überblicksarbeit von Neubauer und Fink (2009) findet sich während der Bearbeitung von einfachen und mittelschwierigen Aufgaben bei weniger intelligenten Personen eine stärkere funktionelle Aktivität in frontalen

Hirnarealen als bei intelligenteren Personen. Bei schwierigen Aufgaben hingegen weisen intelligentere Personen eine stärkere funktionelle Hirnaktivität auf als weniger intelligente Personen.

Die Ergebnisse zu intelligenzbedingen Unterschieden in der funktionellen Hirnaktivität sind aus mehreren Gründen sehr schwierig zu interpretieren. So sind beispielsweise die Vorgehensweisen zur Bildung der Intelligenzgruppen aber auch die verwendeten Aufgaben zwischen den Forschergruppen sehr heterogen. Ein ganz entscheidender Aspekt, der die Vergleich- und Interpretierbarkeit der Ergebnisse bedeutend erschwert, ist die fehlende Berücksichtigung individueller Leistungsunterschiede beziehungsweise die subjektive Aufgabenschwierigkeit. Wird diese nicht berücksichtigt, kann nicht ausgeschlossen werden, dass Unterschiede der funktionellen Hirnaktivität zwischen intelligenteren und weniger intelligenten Personen lediglich aufgrund der niedrigeren beziehungsweise höheren subjektiven Aufgabenschwierigkeit zustande kamen und nicht aufgrund eines spezifischen Unterschiedes in der Aufgabenverarbeitung.

Die Ergebnisse der zwei vorliegenden Studien (Witmer et al., 2018a, 2018b) ergaben sowohl für die Erwachsenen- als auch die Kinderstichprobe eine signifikante Dreifachinteraktion zwischen Hämoglobin Oxygenierung (O_2Hb und HHb), Bedingung (aktive Kontroll- und Experimentalbedingung) und Intelligenz (IQ↑ und IQ↓). Die nachfolgende intelligenzgruppenspezifische Analyse zeigte bei den IQ↑ Gruppen weder während der aktiven Kontroll- noch während der Experimentalbedingung eine funktionelle Hirnaktivität. Bei den IQ↓ Gruppen hingegen fand sich während der Experimentalbedingung das typische Muster der funktionellen Hirnaktivität mit einem Anstieg im O_2Hb bei gleichzeitigem Absinken der HHb Konzentration. Während der aktiven Kontrollbedingung war keine funktionelle Hirnaktivität beobachtbar. Dies bedeutet, dass sich bei subjektiv vergleichbarer Aufgabenschwierigkeit sowohl bei Erwachsenen als auch Kindern intelligenzbedingte, interindividuelle Unterschiede in der funktionellen Hirnaktivität nachweisen lassen (siehe Abbildung 4).

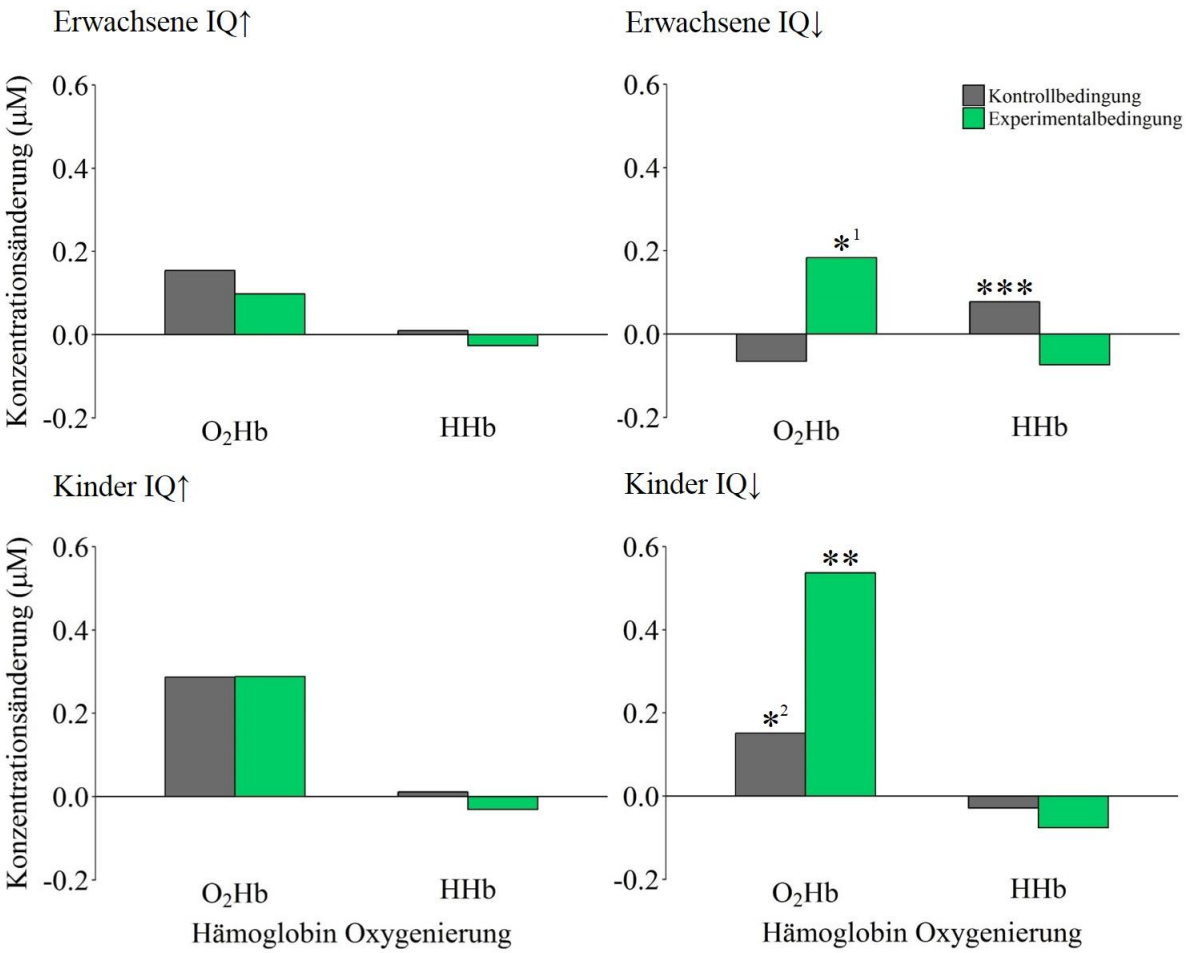

Abbildung 4. Auswirkungen der Intelligenz (IQ) und Bedingung auf die Konzentrationsänderungen im oxygenierten (O_2Hb) und deoxygeniertem (HHb) Hämoglobin bei Erwachsenen und Kindern höherer (IQ↑) und niedrigerer (IQ↓) Intelligenz. Innerhalb der Erwachsenen- als auch der Kinderstichprobe zeigte sich ein signifikanter Unterschied zwischen der aktiven Kontroll- und Experimentalbedingung im O_2Hb. Dieser Unterschied wurde in der Erwachsenenstichprobe auch im HHb signifikant. In der Kinderstichprobe wurde auch der Unterschied zwischen O_2Hb und HHb innerhalb der Experimentalbedingung signifikant. *[1]: Signifikant verschieden zur O_2Hb-Konzentrationsänderung in der aktiven Kontrollbedingung ($p < .05$); *[2]: Signifikant verschieden zur O_2Hb-Konzentrationsänderung in der Experimentalbedingung ($p < .05$); **: Signifikant verschieden zur HHb-Konzentrationsänderung in der Experimentalbedingung ($p < .01$); ***: Signifikant verschieden zur HHb-Konzentrationsänderung in der Experimentalbedingung ($p < .001$).

Die Ergebnisse aus den vorliegenden Studien (Witmer et al., 2018a, 2018b) stimmen mit den Befunden aus älteren Studien überein, die eine negative Korrelation zwischen Intelligenz und funktioneller Hirnaktivität berichteten (Haier et al., 1988; Neubauer et al., 2002; Parks et al., 1988), stehen allerdings im Widerspruch zu neueren Studien, die eine positive Korrelation fanden (Basten et al., 2013; Ebisch et al., 2012; Lee et al., 2006). Basten et al. (2015) analysierten in ihrer Meta-Analyse 16 Studien, die den Zusammenhang zwischen Intelligenz und funktioneller Hirnaktivität mit bildgebenden Verfahren untersucht haben. Die Mehrheit der Studien

wies einen positiven Zusammenhang zwischen Intelligenz und funktioneller Hirnaktivität auf. Allerdings zeigten diejenigen Studien, die verschiedene Areale über das gesamte Gehirn (im Vergleich zu Studien, die nur ganz spezifische ROI untersuchten) analysiert haben, dass dieser Zusammenhang für bestimmte Hirnareale (Graham et al., 2010; Preusse, van der Meer, Deshpande, Krueger & Wartenburger, 2011), in Abhängigkeit der kognitiven Aufgabe (Graham et al., 2010) und kognitiven Prozesse (Fangmeier, Knauff, Ruff & Sloutsky, 2006) sehr spezifisch ist. Basten et al. (2015) betonten ausserdem, dass eine Interpretation dieser Ergebnisse, dahingehend, dass Personen mit höherer Intelligenz kognitive Aufgaben anders verarbeiten als Personen mit niedrigerer Intelligenz nur dann erfolgen sollte, wenn die subjektive Aufgabenschwierigkeit zwischen den Versuchspersonen tatsächlich vergleichbar ist. Sowohl Larson et al. (1995) als auch Dunst et al. (2014) haben in einer PET- beziehungsweise fMRI-Studie zu intelligenzbedingten Unterschieden in der funktionellen Hirnaktivität ebendiese Forderung umgesetzt. Beide Studien nahmen an, dass eine vergleichbare Lösungswahrscheinlichkeit einer Aufgabe bei allen Personen dieselbe subjektive Aufgabenschwierigkeit wiederspiegelt. Larson et al. (1995) verglichen den Glukoseverbrauch während einer kognitiven Aufgabe zwischen intelligenteren und weniger intelligenten Personen bei Aufgaben mit einer Lösungswahrscheinlichkeit von 75%, was sie als „schwierig“ einstuften. Es zeigte sich, dass die intelligenteren Personen eine höhere Glukosestoffwechselrate aufwiesen. Dunst et al. (2014) verglichen intelligentere und weniger intelligente Personen während logischen Denkaufgaben mit einer Lösungswahrscheinlichkeit von 80%. Hier zeigte sich kein Unterschied in der funktionellen Hirnaktivität zwischen beiden Gruppen. Obwohl in den beiden vorliegenden Studien (Witmer et al., 2018a, 2018b) im Gegensatz zu diesen früheren Studien sowohl ein anderes bildgebendes Verfahren, als auch eine andere kognitive Aufgabe und ein anderer Ansatz für die Bestimmung der subjektiven Aufgabenschwierigkeit gewählt wurde, lassen sich die Befunde an diejenigen von Dunst et al. (2014) und Larson et al. (1995) anknüpfen. In der Experimentalbedingung der Arbeitsgedächtnisaufgabe konnten die Erwachsenen im Mittel 88.6% und die Kinder 92.1% der Aufgaben richtig lösen (siehe Tabelle 2). Demzufolge kann die subjektive Aufgabenschwierigkeit für die Versuchspersonen der vorliegenden Studien (Witmer et al., 2018a, 2018b) als tief eingeschätzt werden. Neubauer und Fink (2009) postulierten die Annahme, dass der Unterschied in der funktionellen Hirnaktivität zwischen den Intelligenzgruppen von der Aufgabenschwierigkeit abhängt. Einfache Aufgaben sollten gemäss ihrer Hypothese bei weniger intelligenten Personen zu einer höheren funktionellen Hirnaktivität führen als bei intelligenteren Personen. Bei einer mittleren Aufgabenschwierigkeit zeige sich kein Unterschied in der funktio-

nellen Hirnaktivität zwischen den zwei Intelligenzgruppen und bei schwierigen Aufgaben würden Personen höherer Intelligenz eine höhere funktionelle Hirnaktivität aufweisen als Personen niedrigerer Intelligenz (Neubauer & Fink, 2009). Die Ergebnisse der Kinder- als auch der Erwachsenenstichprobe passen zusammen mit den Ergebnissen von Dunst et al. (2014) und Larson et al. (1995) sehr gut zur postulierten Hypothese von Neubauer & Fink (2009) (siehe Abbildung 5).

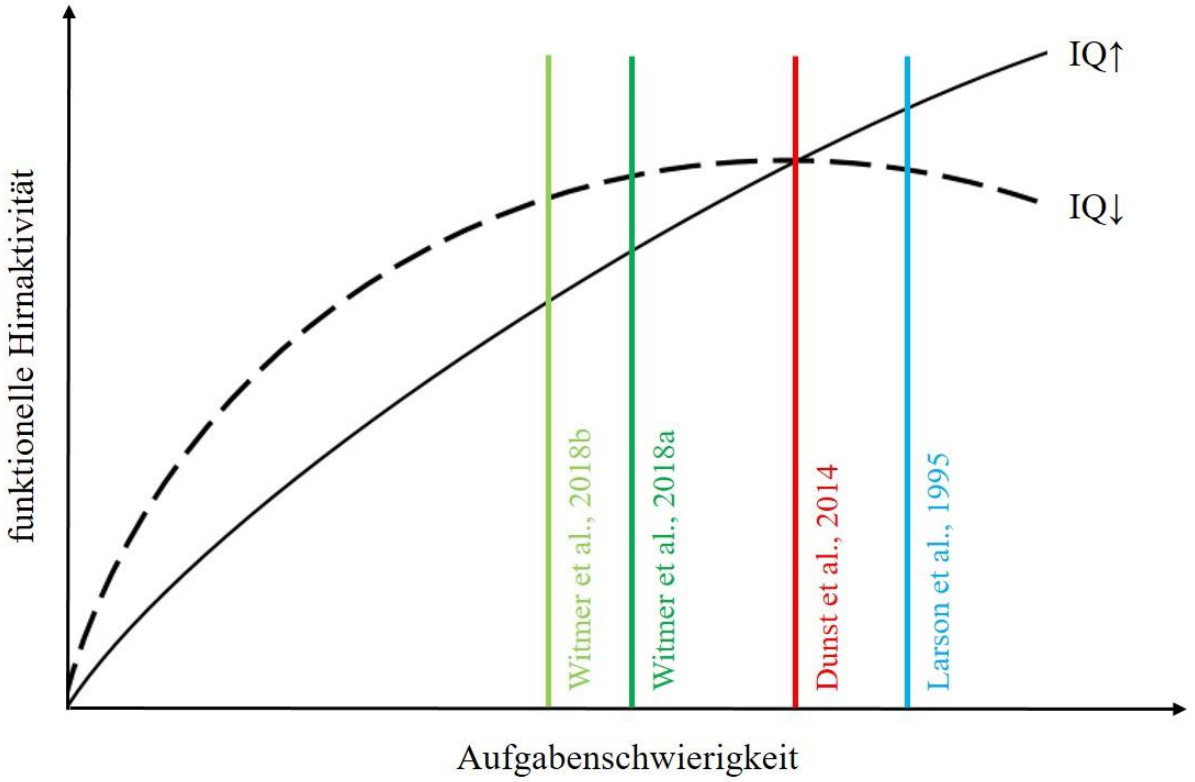

Abbildung 5. Modell des Zusammenhangs zwischen Aufgabenschwierigkeit, funktioneller Hirnaktivität und Intelligenz (nach Neubauer & Fink, 2009). Die farbigen Linien repräsentieren die in den jeweiligen Studien gefundenen Ergebnisse innerhalb des Modells.

Wird der Zusammenhang zwischen Intelligenz und funktioneller Hirnaktivität durch das Geschlecht moduliert?

Bisherige Studien zeigten, dass die funktionelle Hirnaktivität nicht nur durch die Intelligenz sondern zusätzlich auch durch das Geschlecht moduliert wird (Neubauer et al., 2002, 2005; Schmithorst & Holland, 2006; Tang et al., 2010). Neubauer et al. (2002) untersuchten beispielsweise die funktionelle Hirnaktivität mittels Elektroenzephalogramm bei erwachsenen Männern und Frauen während der Bearbeitung von verbalen, numerischen und visuell-räumlichen Aufgaben. Die intelligenzbedingten Unterschiede waren bei Männern in der visuell-räumlichen Aufgabe deutlich ausgeprägter als bei den Frauen. So wiesen die weniger intelligenten

Männer über den gesamten Kortex mehr funktionelle Hirnaktivität auf als intelligenteren Männer wohingegen der Unterschied in der funktionellen Hirnaktivität zwischen den beiden Frauengruppen deutlich geringer ausfiel (Neubauer et al., 2002). Dieselben Befunde wurden drei Jahre später erfolgreich repliziert (Neubauer et al., 2005). Bei beiden Gruppen lag die Lösungswahrscheinlichkeit der Aufgabe bei über 90%, so dass angenommen werden kann, dass es sich um eine einfache Aufgabe gehandelt hat. Allerdings wurde auch in dieser Replikationsstudie die subjektive Aufgabenschwierigkeit nicht berücksichtigt, was zur Folge hatte, dass die Männer in dieser Aufgabe signifikant bessere Leistungen (% korrekter Antworten und kürzere Reaktionszeiten) zeigten als die Frauen was entsprechend die Vergleichbarkeit beider Gruppen erheblich erschwert. Auch mittels fMRI wurden Geschlechtsunterschiede, Intelligenz und funktionelle Hirnaktivität untersucht (Tang et al., 2010). Die Ergebnisse dieser Studie deuten in dieselbe Richtung wie diejenigen von Neubauer et al. (2002, 2005). So zeigte sich bei den Männern im linken präfrontalen Kortex während der Bearbeitung von visuell-räumlichen Aufgaben eine negative Korrelation zwischen Intelligenz und funktioneller Hirnaktivität (r = -.42), bei den Frauen hingegen eine positive Korrelation (r = .16). Obwohl der Unterschied zwischen den zwei Korrelationen nicht signifikant wurde (p = .077) lässt sich dennoch ein Trend hinsichtlich eines Geschlechtsunterschieds erkennen. Auch bei Kindern (Schmithorst & Holland, 2006) und Jugendlichen (Dunst, Benedek, Bergner, Athenstaedt & Neubauer, 2013) unterschiedlichen Alters wurde der Zusammenhang zwischen Intelligenz, Geschlecht und funktioneller Hirnaktivität untersucht. In der fMRI Studie von Schmithorst & Holland (2006) wurden über 300 Kinder im Alter zwischen 5 und 18 Jahren getestet. Die Kinder bearbeiteten eine Aufgabe, bei der sie nach dem akustischen Input eines Nomens (z. B. «Ball») zu diesem Nomen passende Verben generieren mussten (z. B. «werfen»). Die Aufgabe wurde so ausgewählt, dass sie sowohl von den jüngeren als auch den älteren Kindern problemlos gelöst werden konnte. Allerdings sollte die Aufgabe still gelöst werde, so dass keine Kontrolle über die Leistung möglich war. Schmithorst & Holland (2006) fanden sowohl für Knaben und Mädchen als auch für unterschiedliche Altersgruppen differenzielle Befunde hinsichtlich des Zusammenhangs zwischen Intelligenz und funktioneller Hirnaktivität im linken mittleren und superioren frontalen Gyrus. Während bei den jüngeren Mädchen (< 13 Jahre) keine Korrelation der funktionellen Hirnaktivität mit dem IQ auftrat, fand sich bei den älteren Mädchen (> 13 Jahre) eine positive Korrelation. Bei den Knaben zeigte sich ein umgekehrter Effekt. Bei den ganz jungen Knaben (< 9 Jahre) war die Korrelation zwischen Intelligenz und funktioneller Hirnaktivität positiv, bei den älteren Knaben (> 13 Jahre) hingegen negativ. Dunst et al. (2013) untersuchten Mittels Elektroenzephalogramm

Jugendliche im Alter zwischen 15 und 18 Jahren während der Bearbeitung einer mentalen Rotationsaufgabe. Sie fanden bei den Knaben eine signifikant negative Korrelation zwischen Intelligenz und funktioneller Hirnaktivität insbesondere in der linken Hemisphäre wohingegen diese Korrelation bei den Mädchen positiv ausfiel. Sowohl die Ergebnisse der älteren Knaben und Mädchen (> 13 Jahre) von Schmithorst & Holland (2006) als auch diejenigen von Dunst et al. (2013) stimmen mit den Befunden bei Erwachsenen von Tang et al. (2010) und Neubauer et al. (2002, 2005) überein. Zusammenfassend kann folglich festgehalten werden, dass die Geschlechtsunterschiede hinsichtlich des Zusammenhangs zwischen Intelligenz und funktioneller Hirnaktivität ab einem Alter von 13 Jahren relativ einheitlich sind. So wiesen Männer und Knaben einen negativen Zusammenhang und Frauen und Mädchen einen positiven Zusammenhang zwischen Intelligenz und funktioneller Hirnaktivität auf.

Um zu überprüfen, ob der Zusammenhang zwischen Intelligenz und funktioneller Hirnaktivität auch in den beiden Stichproben der vorliegenden Studien (Witmer et al., 2018a, 2018b) durch das Geschlecht beeinflusst wird, wurden für beide Geschlechter in beiden Stichproben separate Varianzanalysen mit den Faktoren Hämoglobin Oxygenierung (O_2Hb und HHb), Bedingung (aktive Kontroll- und Experimentalbedingung) und Intelligenz (IQ↑ und IQ↓) berechnet. In der Erwachsenenstichprobe zeigten sich weder bei den Männern noch bei den Frauen signifikante Haupteffekte. Bei den Männern wurde sowohl die Interaktion zwischen Hämoglobin Oxygenierung und Bedingung [$F(1, 19) = 18.23$, $p < .001$, $\eta_p^2 = .490$] als auch die Interaktion zwischen Hämoglobin Oxygenierung, Bedingung und Intelligenz [$F(1, 19) = 5.74$, $p = .027$, $\eta_p^2 = .232$] signifikant. Die Analyse der Frauengruppe ergab keine signifikanten Interaktionen. Um die signifikante Dreifachinteraktion der Männergruppe besser interpretieren zu können, wurden für die IQ↑ und die IQ↓ Gruppe der Männer zwei separate Varianzanalysen mit den Faktoren Bedingung und Hämoglobin Oxygenierung berechnet. Die Haupteffekte wurden weder in der IQ↑ noch in der IQ↓ Gruppe signifikant. Die Interaktion zwischen Hämoglobin Oxygenierung und Bedingung wurde nur in der IQ↓ Gruppe signifikant [$F(1, 9) = 19.88$, $p = .002$, $\eta_p^2 = .688$]. Post-Hoc Paarvergleiche (korrigiert nach Bonferroni-Holm; Holm, 1979) in der IQ↓ Gruppe zeigten, dass die relative Konzentration von O_2Hb in der aktiven Kontrollbedingung signifikant tiefer war als in der Experimentalbedingung [$t(9) = 3.50$, $p = .020$, $d = 0.77$]. Das relative Konzentration des HHb hingegen war in der aktiven Kontrollbedingung signifikant höher als in der Experimentalbedingung [$t(9) = 4.43$, $p = .007$, $d = 1.03$] (siehe Abbildung 6). In der Kinderstichprobe wurde der Haupteffekt Hämoglobin Oxygenierung sowohl bei den Knaben [$F(1, 18) = 8.29$, $p = .010$, $\eta_p^2 = .315$] als auch bei den Mädchen [$F(1, 20) = 6.02$,

p = .023, η_p^2 = .231] signifikant. Dies bedeutet, dass sich bei den Kindern die O_2Hb Konzentration während der Bearbeitung der Aufgabe deutlich stärker verändert als die HHb Konzentration. Die Haupteffekte Bedingung und Intelligenz wurden weder in der Knaben- noch in der Mädchengruppe signifikant. Die Interaktion zwischen Hämoglobin Oxygenierung und Bedingung wurde nur in der Mädchengruppe signifikant [F(1, 20) = 5.42, p = .031, η_p^2 = .213]. Die Dreifachinteraktion zwischen Hämoglobin Oxygenierung, Bedingung und Intelligenz wurde weder in der Knaben- [F(1,18) = 3.24, p = .089, η_p^2 = .153], noch in der Mädchengruppe [F(1, 20) = 0.95, p = .341, η_p^2 = .045] signifikant.

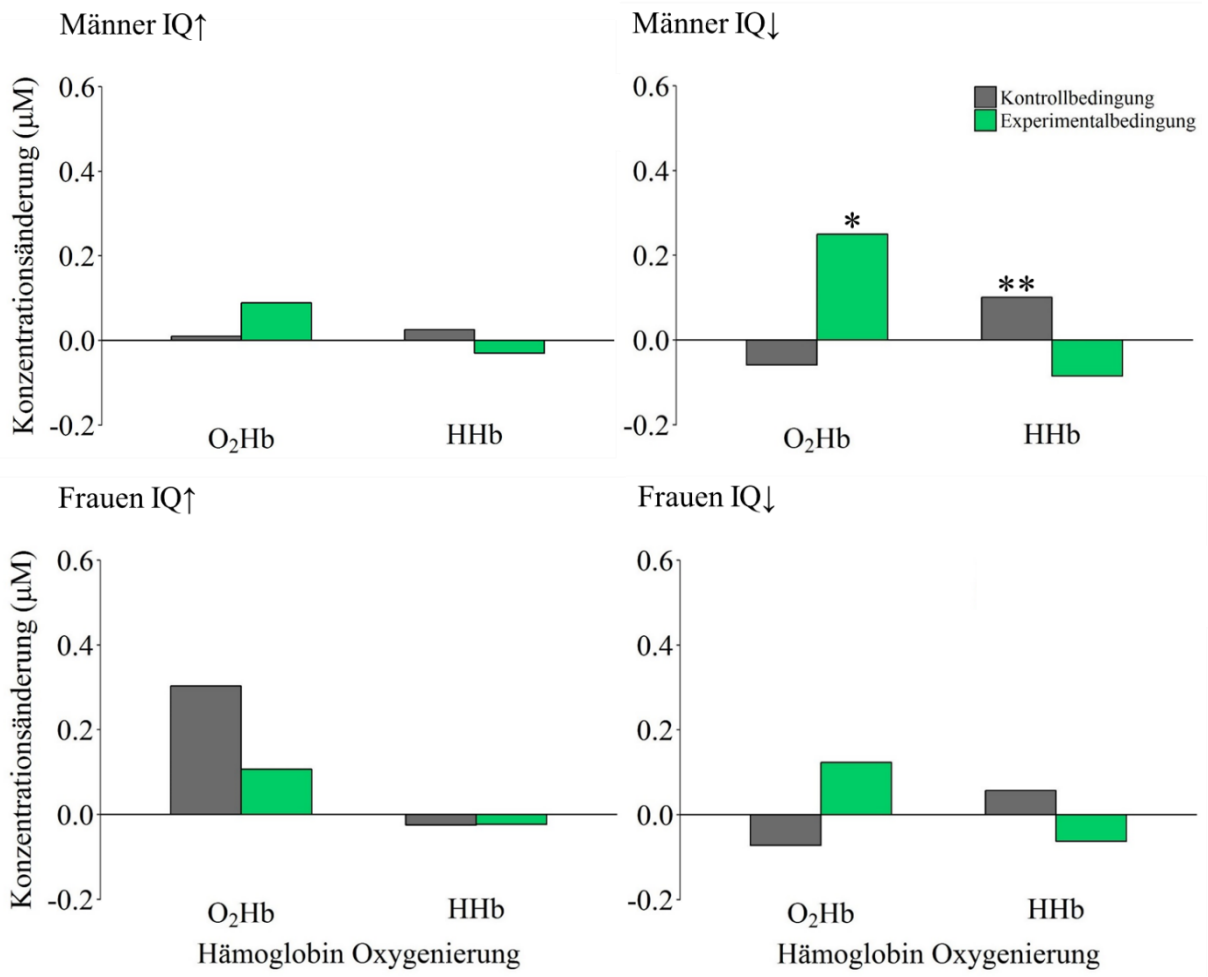

Abbildung 6. Auswirkungen der Intelligenz (IQ) und Bedingung auf die Konzentrationsänderungen im oxygenierten (O_2Hb) und deoxygeniertem (HHb) Hämoglobin bei Männern und Frauen höherer (IQ↑) und niedrigerer (IQ↓) Intelligenz. Innerhalb der Männerstichprobe mit IQ↓ zeigte sich sowohl im O_2Hb als auch im HHb ein signifikanter Unterschied zwischen der aktiven Kontroll- und Experimentalbedingung. Diese Unterschiede wurden weder in der Gruppe der Männer mit IQ↑ noch bei beiden Frauengruppen signifikant. *: Signifikant verschieden zur O_2Hb-Konzentrationsänderung in der aktiven Kontrollbedingung (p < .05); **: Signifikant verschieden zur HHb-Konzentrationsänderung in der Experimentalbedingung (p < .01).

Für die Interpretation dieser Ergebnisse ist es wichtig, die geringe Fallzahl pro Gruppe (N = 9-12) zu berücksichtigen (Button et al., 2013). Die Resultate deuten darauf hin, dass die stärkere funktionelle Hirnaktivität, die bei der geschlechtergemischten Stichprobe niedrigerer Intelligenz beobachtet wurde insbesondere durch die Männer verursacht wurde. Dass derselbe Effekt bei den Kindern nicht gefunden wurde, könnte damit zusammenhängen, dass in dieser Stichprobe Kinder im Alter zwischen 11 und 13 Jahren gemessen wurden. Entsprechend den Befunden von Schmithorst & Holland (2006), zeigt sich ein einheitlicher geschlechtsbedingter Unterschied zwischen Intelligenz und funktioneller Hirnaktivität erst ab einem Alter von 13 Jahren. Gemäss Neubauer et al. (2002, 2005) und Tang et al. (2010) ist die Richtung und Ausprägung des Geschlechtsunterschieds auch vom Aufgabentyp abhängig. So war der Unterschied der funktionellen Hirnaktivität zwischen intelligenteren und weniger intelligenten Männern bei visuell-räumlichen (Dunst et al., 2013; Neubauer et al., 2002, 2005; Tang et al., 2010), nicht aber bei verbalen (Neubauer & Fink, 2003; Neubauer et al., 2005) oder numerischen (Tang et al., 2010) Aufgaben zu finden.

ZUSAMMENFASSUNG DER BEFUNDE

Mit den beiden vorliegenden Studien (Witmer et al., 2018a, 2018b) konnte gezeigt werden, dass fNIRS ausreichend sensitiv ist, um spezifische visuell-räumliche Arbeitsgedächtnisprozesse in einem für die ebendiese Arbeitsgedächtnisprozesse wichtigen frontalen Hirnareal (Brodmann Areal 8) nachzuweisen. Des Weiteren war es mittels fNIRS möglich, intelligenzbedingte Unterschiede der funktionellen Hirnaktivität zu messen. Bei Kindern im Alter zwischen 11 und 13 Jahren und jungen Erwachsenen im Alter zwischen 18 und 24 Jahren konnte gezeigt werden, dass Personen niedrigerer Intelligenz im Vergleich zu Personen höherer Intelligenz eine stärkere funktionelle Hirnaktivität während der Bearbeitung einer subjektiv einfachen, visuell-räumlichen Arbeitsgedächtnisaufgabe aufweisen. Des Weiteren gab es klare Hinweise darauf, dass dieser Zusammenhang zwischen Intelligenz und funktioneller Hirnaktivität durch das Geschlecht moduliert wurde. So zeigte sich zwischen den Männern mit IQ↑ und denjenigen mit IQ↓ ein deutlicher Unterschied in der funktionellen Hirnaktivität während der Bearbeitung der visuell-räumlichen Arbeitsgedächtnisaufgabe, nicht aber bei den Frauen.

GRENZEN DER VORLIEGENDEN UNTERSUCHUNGEN

Obwohl in den beiden Studien die extrazerebrale Durchblutung durch die Verwendung von kurzen Kanälen aus den kortikalen Daten regressiert wurde, war die Umsetzung noch nicht optimal. Die Analyse der Korrelationen zwischen den kurzen und längeren Kanälen hat gezeigt,

dass die Korrelation zwischen denjenigen Kanälen am höchsten war, die die kürzeste Distanz zueinander aufwiesen. Entsprechend wurde der Kanal 1 am stärksten, der Kanal 2 am zweitstärksten und der Kanal 3 am wenigsten stark korrigiert. Die Korrektur des kortikalen Signals durch das extrazerebrale Signal erfolgte folglich nicht in allen drei analysierten Kanälen gleich gut. Eine gleichmässigere Verteilung der kurzen Kanäle hätte möglicherweise auch das Signal-Rausch-Verhältnis der weiteren gemessenen Kanäle (4-16) verbessert, so dass auch diese das strenge Qualitätskriterium der negativen Korrelation zwischen O_2Hb und HHb hätten erfüllen und entsprechend in die Analysen hätten miteinbezogen werden können.

In zukünftigen Studien sollte deshalb versucht werden, das Signal jedes längeren Kanals mit dem Signal eines sehr nahe liegenden kurzen Kanals zu korrigieren. Der Einschluss mehrerer Kanäle in die Analyse wäre dahingehend interessant, als dass dadurch Vergleiche der funktionellen Hirnaktivität in unterschiedlichen Arealen möglich wären. Dies wiederum würde die Prüfung weiterführender Fragestellungen ermöglichen. So könnte es zum Beispiel sehr interessant sein, mittels fNIRS zu prüfen, ob intelligenzbedingte Unterschiede in der funktionellen Hirnaktivität in mehreren Arealen auftreten und welche Richtung die Effekte in unterschiedlichen Arealen aufweisen.

FAZIT UND AUSBLICK

Die Ergebnisse der vorliegenden Studien (Witmer et al., 2018a, 2018b) und zusätzlichen Analysen im Rahmen dieses Mantelpapiers haben aufgezeigt, dass die fNIRS eine sehr gute Methode ist, um differenzierte Fragestellungen zu untersuchen. Die Befunde waren replizierbar und liessen sich auf eine andere Stichprobe generalisieren. Zwei zentrale methodische Aspekte wie die Messung von kurzen Kanälen zur Signalkorrektur der längeren Kanäle (Saager & Berger, 2005; Tachtsidis & Scholkmann, 2016) und die sorgfältige Korrektur von Bewegungsartefakten (Metz, Wolf, Achermann & Scholkmann, 2015; Scholkmann et al., 2010) wurden in beiden Studien umgesetzt. Allerdings zeigte die methodenspezifische fNIRS Forschung in den letzten Jahren, dass auch weitere Aspekte das fNIRS Signal beeinflussen können. So wird empfohlen, während der fNIRS Messung weitere systemische Prozesse wie die Atmung (Anderson et al., 2014; Boas et al., 2004; Holper et al., 2014; Pfeifer et al., 2018), den Blutdruck (Bauernfeind, Wriessnegger, Daly & Müller-Putz, 2014; Boas et al., 2004; Kirilina et al., 2012; Vermeij, Meel-van den Abeelen, Kessels, van Beek & Claassen, 2014) und die Bewegung (Virtanen, Noponen, Kotilahti, Virtanen & Ilmoniemi, 2011) zu messen und anschliessend bei der Korrektur des kortikalen Signals zu berücksichtigen. Eine aktuelle Studie konnte auch nachweisen, dass farbiges Licht (wie es zum Beispiel von einem Testbildschirm emittiert wird) das

fNIRS Signal beeinflussen kann (Metz, Klein, Scholkmann & Wolf, 2017). Für psychologisch orientierte fNIRS Studien, die oft sehr aufwändige Studiendesigns aufweisen und der Forderung nach grösseren Stichprobenumfängen bei bildgebenden Verfahren (Button et al., 2013) nachkommen wollen, sind viele der methodischen Empfehlungen aktuell (noch) nicht realistisch umsetzbar. Dies zeigt sich beispielsweise daran, dass erst die neuste Generation der NIRS-Geräte standardmässig die Möglichkeit bietet, kurze Kanalabstände zu messen. Ein wichtiges Ziel für die Zukunft wäre, dass es eine klare Standardisierung hinsichtlich des methodischen Vorgehens und der Auswertung der Daten und einen besseren interdisziplinären Austausch im Bereich der fNIRS Forschung gibt. Dies würde den Vergleich von Ergebnissen zwischen Forschungsgruppen ermöglichen und die exakte Replikation von Studien erleichtern. Eine anwendungsorientierte methodische Standardisierung könnte sich sehr lohnen, da fNIRS dank den Vorteilen gegenüber anderen bildgebenden Verfahren auch sehr interessante Möglichkeiten für Datenerhebungen mit realitätsnahen Aufgabenstellungen und eine unkomplizierte Messung von Kindern und klinischen Stichproben ermöglicht.

Aus den Ergebnissen der vorliegenden Studien (Witmer et al., 2018a, 2018b) und dieses Mantelpapiers lassen sich einige wichtige Empfehlungen für zukünftige Forschung ableiten. So sollten Studien zu intelligenzbedingen Unterschieden der funktionellen Hirnaktivität immer die subjektive Aufgabenschwierigkeit berücksichtigen. Dies würde die Vergleichbarkeit der Ergebnisse zwischen den Intelligenzgruppen, zwischen unterschiedlichen Aufgaben aber auch zwischen verschiedenen Studien deutlich erleichtern. Des Weiteren sollte für ebensolche Fragestellungen immer auch das Geschlecht berücksichtigt werden, da sich gezeigt hat, dass die Effekte in Abhängigkeit des Geschlechts eine andere Richtung aufweisen. Studien, die beabsichtigen, den Einfluss des Geschlechts auf den Zusammenhang zwischen Intelligenz und funktioneller Hirnaktivität zu untersuchen, sollten idealerweise auch unterschiedliche Aufgabentypen verwenden und unterschiedliche Altersgruppen messen, da beide Aspekte zusätzlich zum Geschlecht die Richtung des Effekts beeinflussen. Obwohl bereits viele Studien den Zusammenhang zwischen Intelligenz und funktioneller Hirnaktivität untersucht haben, bleibt bisher ungeklärt, wie genau die kognitiven Verarbeitungsprozesse bei Personen unterschiedlicher Intelligenz ablaufen. Ein vielversprechender Ansatz zur Beantwortung dieser Frage ist die Untersuchung funktioneller Netzwerke im Gehirn (Park & Friston, 2013), wodurch ein vertieftes Verständnis der kognitiven Prozesse erreicht werden kann (McIntosh, 2004; Poldrack, 2006; Yeo et al., 2011).

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The Validity of Functional Near-Infrared Spectroscopy Recordings of Visuospatial Working Memory Processes in Humans

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Abstract: Functional near infrared spectroscopy (fNIRS) is increasingly used for investigating cognitive processes. To provide converging evidence for the validity of fNIRS recordings in cognitive neuroscience, we investigated functional activation in the frontal cortex in 43 participants during the processing of a visuospatial working memory (WM) task and a sensory duration discrimination (DD) task functionally unrelated to WM. To distinguish WM-related processes from a general effect of increased task demand, we applied an adaptive approach, which ensured that subjective task demand was virtually identical for all individuals and across both tasks. Our specified region of interest covered Brodmann Area 8 of the left hemisphere, known for its important role in the execution of WM processes. Functional activation, as indicated by an increase of oxygenated and a decrease of deoxygenated hemoglobin, was shown for the WM task, but not in the DD task. The overall pattern of results indicated that hemodynamic responses recorded by fNIRS are sensitive to specific visuospatial WM capacity-related processes and do not reflect a general effect of increased task demand. In addition, the finding that no such functional activation could be shown for participants with far above-average mental ability suggested different cognitive processes adopted by this latter group.

Keywords: fNIRS; visuospatial working memory capacity; validity; sensitivity; specificity; subjective task demand; mental ability; duration discrimination

1. Introduction

In the past 30 years, research on cognitive functioning has been complemented by neuroimaging methods that measure the magnitude of functional activation and the brain areas involved in specific aspects of information processing [1]. The techniques used most frequently in this research area are positron emission tomography (PET) and functional magnetic resonance imaging (fMRI). More recently, functional activation has also been measured with functional near-infrared spectroscopy (fNIRS) [2,3]. The advantage of fNIRS over PET and fMRI is its compact measurement system that is relatively robust to motion artifacts, which enable its use outside of a scanner in a variety of experimental settings. Functional activation requires oxygen, which leads to increased cerebral blood flow due to neurovascular coupling and changes in the local concentrations of two types of hemoglobin (Hb): oxygenated (O_2Hb) and deoxygenated (HHb) [4]. Near-infrared light of different wavelengths is radiated into the brain tissue where it is absorbed and scattered, and the unabsorbed light is measured. This allows for continuous

and noninvasive monitoring and quantification of the concentration changes of O_2Hb and HHb in the cortex. Several studies comparing fNIRS and fMRI data have reported strong correlations between their signals [5–7]. Furthermore, fNIRS is sensitive to cognitive state (e.g., resting state vs. task performance) and cognitive task load [8,9]. These results provide converging evidence that fNIRS is a reliable method that can be used to measure hemodynamic responses in the cortex under specific conditions.

Many neuroimaging studies of information processing have investigated functional activation during the processing of working memory (WM) tasks [6,10–12]. WM refers to the capacity-limited system responsible for the simultaneous manipulation and storage of information [13–15]. WM capacity is usually assessed with complex span tasks in which the participants are required to remember and mentally process several stimuli over a brief period [16]. However, the use of complex span tasks results in impure measures of WM [17], which indicates that the processing of these tasks requires multiple processes (e.g., perception, attention, storage and motor response). Neuroimaging studies illustrate this with different processes resulting in functional activation in different brain areas (e.g., [18]). A comparison of storage-only and storage-plus-processing tasks conducted by Smith and Jonides [19] revealed functional activation in areas related to the content of a given task and additional functional activation in the prefrontal cortex in storage-plus-processing tasks. The results of a large meta-analysis of WM tasks in fMRI experiments conducted by Rottschy and colleagues [11] had similar conclusions. They suggested that a bilateral frontoparietal core network sustains the basal processes required for most WM-related cognitive functions. Differences in functional activation become apparent according to task-induced cognitive load, task type (e.g., memory of location vs. stimulus identity in visual WM tasks) and type of required recall (e.g., verification, matching or reproduction). For example, tasks requiring memory of location (compared to stimulus identity) and tasks requiring reproduction (compared to verification and matching) result in more functional activation in the posterior superior frontal gyrus [11].

The goal of measuring functional activation resulting exclusively from WM-specific processes has two challenges. The first challenge is the differentiation of functional activation between specific WM-related processes and general WM-unspecific processes, such as stimulus encoding or response selection. To address this first problem, an experimental condition that is able to disentangle WM-specific and WM-unspecific processes is needed [20]. One possible solution for this issue is the so-called subtraction approach [21], which involves an active control condition in which most perceptual and response-related processes are the same as those in the experimental condition, while the WM-specific process of interest is only required for the experimental task. Thus, the differences in functional activation between the experimental and active control conditions can then be attributed to the WM-specific processes of interest.

If, based on the subtraction approach, functional activation can be assigned to the WM-specific processes in the experimental condition, a second challenge emerges. More precisely, it remains unclear whether the observed differences in functional activation between the active control condition and experimental condition reflect the specific WM-related processes or a more general increase in task demand. Therefore, ensuring that the observed changes in functional activation are indeed caused by the specific WM-related task demands rather than by a general increase in task demand, which can be elicited by any task, is important.

To distinguish functional activation induced by a specific WM-related process from that induced by general task-independent effects of increasing task demand, an additional comparison task that is functionally unrelated to WM and that has a task demand comparable to that of the WM task is required. In the present study, we chose to use duration discrimination (DD) as the comparison task. With this task, the participant is required to watch to two successively presented light flashes and to decide which light flash was longer. The discrimination of very brief intervals in the range of milliseconds has been proposed to depend on sensory-perceptual rather than higher-order cognitive processes [22,23]. This suggestion was confirmed by experimental [24,25] and neuropharmacological studies (for a concise review, see [26]), neurocomputational approaches [27] and neuroimaging studies [28]. In line

with these results is a meta-analysis that showed that processes involving timing in the range of milliseconds mainly recruit subcortical networks in the basal ganglia and cerebellum [29].

To enable comparisons of the functional activation produced by two different tasks, ensuring that the subjective level of task difficulty for a given individual, and thus the level of task demand elicited by the two tasks, is about the same for both tasks is essential. This can be achieved by using an adaptive procedure to adjust the individual variability of performance across different tasks to a set criterion level [30,31]. Even more importantly, adopting a subjective level of task difficulty is a crucial prerequisite for comparing task-specific functional activation resulting from the same task in multiple individuals. This is particularly important as the interindividual variability of performance within a sample can be large. The lack of a control for a subjective level of task difficulty inevitably implies that some individuals will experience increased task demands, while others will experience decreased task demands. These differences in task demand can produce large differences in functional activation, even within a given experimental condition [32]. From this perspective, the adaptive approach ensures that all participants process the task with subjectively similar levels of task difficulty. Thus, the task demands required to solve the task should be comparable among individuals.

Various neuroimaging studies have reported negative correlations between brain glucose metabolism and mental ability. That is, individuals with higher ability (HA) show lower brain glucose metabolism rates than individuals with lower ability (LA) do when they perform the same cognitive tasks [33] (for a concise review, see [34]). Given the close relationship between mental ability and WM [16,35], it cannot ruled out that also O_2Hb and HHb concentration changes, as assessed by fNIRS, could be effectively modulated by individual differences in mental ability. For this reason, participants' individual level of mental ability was controlled for in the present study.

Thus, the major aim of the present study was to investigate whether fNIRS was suitable for measuring WM-specific differences in the concentration changes of Hb oxygenation irrespective of the concurrently ongoing processes that are less specific for WM capacity. More precisely, we probed whether the changes in functional activation observed during the performance of a WM task can be considered specific for WM-related processes rather than subsidiary processes, such as perceptual encoding or motor processes. For this purpose, we compared activation elicited by an experimental WM condition and active control condition. Furthermore, we included DD as an additional task, as well as a corresponding active control condition, which was functionally unrelated to WM capacity. To ensure that the subjective levels of task difficulty were the same for all participants and both tasks, an adaptive procedure was applied for the WM and the DD task.

If the changes in functional activation observed with the WM task were mostly task-unspecific and therefore only reflected the general task demands that were induced by task difficulty, the same pattern of functional activation should be observed during the performances of both the WM and DD tasks. However, if functional activation is observed in a specific cortical area during the performance of the WM task, but not during the performance of the DD task, the functional activation might be directly related to WM capacity. Finally, by comparing two groups of individuals with different levels of mental ability, we assessed how much the functional activation was effectively modulated by individual differences in mental ability.

2. Materials and Methods

2.1. Participants

In the first session, the participants were screened for mental ability with the German adaptation of Cattell's Culture Fair Test 20-R [36]. To ascertain the groups with the extremes of mental ability, we calculated that a difference of 16 IQ points was required between the HA and LA groups to avoid any overlap of the 95% confidence intervals. Therefore, we selected study participants with IQs lower than or equal to 112 (LA group: IQ range, 90–112) and IQs higher than or equal to 130 (HA group: IQ range, 130–145). The LA group consisted of 21 participants (11 women; age range,

20–24 years; mean ± standard deviation of age, 21.9 ± 1.5 years), and the HA group consisted of 22 participants (11 women; age range, 18–24 years; mean ± standard deviation of age: 20.8 ± 2.1 years). All participants were right-handed with normal hearing and normal or corrected-to-normal vision. According to self-reports, all were nonsmokers without a history of psychiatric or neurological illness, serious head injury or psychotropic drug use. For participation in the study, they received 100 Swiss Francs. The participants provided written informed consent after they were given detailed explanations of the study protocol and NIRS recording procedures. The study was approved by the ethics committee of the Faculty of Human Sciences of the University of Bern (Bern, Switzerland) (date of approval: 29 July 2014; project identification code: No. 2014-6-880651).

2.2. Tasks

2.2.1. Visuospatial WM Task

A combined version of the Matrix Task [37] and Patterns-Memory Task [38] was used to quantify individual visuospatial WM spans. The task was fully computer-controlled and programmed with E-Prime experimental software (version 2.0, Psychology Software Tools, Inc., Sharpsburg, PA, USA). Each trial started with the presentation of a fixation cross for 500 ms and then a black 4 × 4 grid (13.2 × 13.2 cm) with 16 white squares (empty grid) in the center of a touchscreen monitor. In the first condition, two of the 16 squares were successively blackened in a pseudorandom order for 1000 ms each. The participants were required to memorize the location and order of appearance of the black squares. A question mark was then displayed for 1000 ms, and then, an empty grid that was used as an input template for the participant's response was displayed. The participants were instructed to touch the two squares on the empty grid that were previously black on the touchscreen monitor in reverse order with their right index finger. The task began with a block of four trials with a span of two squares to be memorized. The second block consisted of four trials with a span of three squares to be memorized; the third block consisted of four trials with a span of four squares to be memorized, and so on. The span was increased after each block by one additional square if the participant was able to correctly solve at least three trials within a block. The number of squares in the last edited block in which this criterion was fulfilled corresponded to the individual's WM span, which was the dependent variable in this task.

2.2.2. DD Task

To quantify temporal sensitivity in the range of milliseconds, a visual DD task was used. The task was fully computer-controlled and programmed with E-Prime experimental software (Version 2.0, Psychology Software Tools, Inc., Sharpsburg, PA, USA). The stimuli were a 100-ms light flash (the standard interval) and a light flash with variable duration (the comparison interval) that were presented as a computer-controlled red light-emitting diode (diameter, 0.38°; viewing distance, 60 cm; luminance, 68 cd/m^2) that was positioned at eye level.

The task consisted of 32 trials, with each trial consisting of a standard interval and comparison interval with an interstimulus interval of 900 ms. The duration of the comparison interval varied according to the weighted up-down method [39], which is an adaptive psychophysical procedure. "Adaptive" means that the difference in the stimulus durations between the constant standard stimulus and variable comparison stimulus varied from trial to trial depending on the participant's previous response. Correct responses resulted in a decrease in the difference between the standard and comparison stimuli, while incorrect responses made the task easier by increasing this difference.

The first comparison interval was 135 ms. During the first six trials, the differences between the standard and comparison intervals were decreased by 5 ms after a correct response and increased by 15 ms after an incorrect response. For the subsequent trials, the step sizes were 3 ms and 9 ms, respectively. After each trial, the participants had to decide whether the first or second interval was longer by pressing one of two designated response keys. Visual feedback was given immediately after the participant's response was presented for 1500 ms. The next trial started 800 ms after the feedback.

As a psychophysical indicator of performance, the 75%-difference threshold, which was defined as the difference between the standard and comparison stimuli at which a given participant produced 75% correct responses, was calculated. With this procedure, a higher temporal sensitivity was indicated by smaller threshold values. A detailed description of the psychophysical procedure has previously been reported by Rammsayer [40].

2.2.3. fNIRS Tasks

The participants were instructed to sit quietly with their eyes open during the resting phase. All instructions were given orally via headphones (CX 5.00G, Sennheiser electronic GmbH & Co. KG, Wedemark, Germany). Before each task, verbal instructions were given, and then, several practice trials followed. The fNIRS measurements started during a resting phase of 45 s, which was followed by either the DD or WM task. The order of the tasks was counterbalanced across participants. Both tasks consisted of four blocks of the active control task and four blocks of the experimental task. The processing of the experimental tasks required WM-specific (for the visuospatial WM task) and DD-specific (for the DD task) processes, as well as task-unspecific processes, such as attention, perception and encoding of the stimuli, response selection and execution of the motor response. In contrast, the processing of the control tasks consisted of the same processes except for those of the WM-specific and DD-specific processes. With the subtraction approach, this procedure allowed for the identification of WM-/DD-specific changes in Hb oxygenation concentration [20,21,41].

The control and experimental blocks were presented in alternating order, and they lasted for 40 s each. All blocks were separated by a resting phase. To reduce the influence of Mayer waves, which are spontaneous oscillations in blood flow that confound fNIRS signals [42] and prevent entrainment of the blood flow changes due to rhythmic changes, the duration of the resting phases were randomly varied from 25–40 s. Within each task, the order of the active control and experimental blocks was also counterbalanced across the participants (see Figure 1).

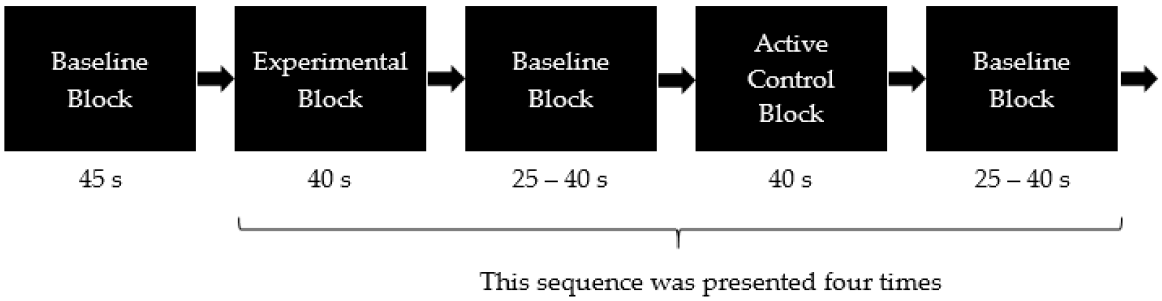

Figure 1. Illustration of the block design, which contained eight baseline blocks (resting phases), four experimental blocks and four active control blocks. After the baseline block, participants started either with an experimental or an active control block (the order was counterbalanced across participants).

fNIRS visuospatial WM task: The stimuli and procedures were identical to those in the ordinary WM task, except that no adaptive procedure was applied. Thus, in the experimental condition, each participant performed the task with his/her individual WM span that was determined in the previous experimental session. In the active control condition, the same number of squares was blackened as in the experimental condition, but in a systematic order (from top to bottom or left to right). Thus, the task demands on WM were substantially reduced. The dependent variable, the percentage of correctly solved trials, was calculated.

fNIRS DD task: The stimuli and procedures were identical to those in the ordinary DD task, except that no adaptive procedure was applied and no visual feedback was given. In the experimental condition, the duration of the standard interval was 100 ms, while the comparison interval was 100 ms plus the individual threshold value that was determined in the previous experimental session (e.g., if someone had a discrimination threshold of 28 ms, the duration of the comparison interval would be 128 ms). For the

active control blocks, the durations of the standard and comparison intervals were held constant at 100 ms and 360 ms, respectively. This difference in duration between the standard and comparison intervals was well beyond the participants' DD thresholds and therefore easy to distinguish for all participants. The dependent variable, the percentage of correct responses, was calculated.

2.3. fNIRS Recordings

The fNIRS data were acquired with a FOIRE-3000 multichannel system (Shimadzu Corporation, Kyoto, Japan) at a sampling rate of 7.69 Hz. The FOIRE-3000 system included eight light-emitter and eight light-detector probes. First, the Nz, Fpz, Cz, Oz, A1, A2 and T3 landmarks were measured and marked on the scalp according to the 10–20 positioning system [43]. The 16 probes were subsequently mounted on the left forehead with a purpose-built probe holder (see Figure S1). As shown in Figure 2, Detector 2 was placed at Fpz, and Source 1 and Detector 1 were located on an imaginary line that extended in the direction of Cz, while the bottom row of the probes (with Sources 4 and 8 and Detectors 2, 4, 5, 7 and 8) were located on an imaginary line that extended in the direction of T3. For each participant, the three-dimensional spatial positions of the marked points on the scalp and each probe in the probe holder were measured using a FASTRAK® 3D magnetic field digitizer (Polhemus, Colchester, VT, USA) and 3D position measurement system software (Version 4.1.0.0, Shimadzu Corporation, Kyoto, Japan). This procedure facilitates the determination of the precise channel positions despite variations in head size and shape [44]. We modified our standard probe holder to allow for the measurement of short channels. With these, the influence of the superficial skin and scalp tissue can be reduced, and the sensitivity for the cortex therefore increases [41]. We arranged the probe holder so that it included four short channels (source-detector distance, ~15 mm), 16 longer channels (source-detector distance, ~30 mm) and six long channels (source-detector distance, ~42 mm). Short channel regression was applied to diminish superficial influences, such as hemodynamic fluctuations in the scalp [45] in both O_2Hb and HHb [46]. Each long channel was regressed with the closest short channel (see Figure 2). The short channel regression was only applied if the correlation between the time series of the two signals was sufficient such that $R^2 > 0.1$, which is a criterion adapted from Gagnon et al. [47]. The short channels were not included in subsequent statistical analyses.

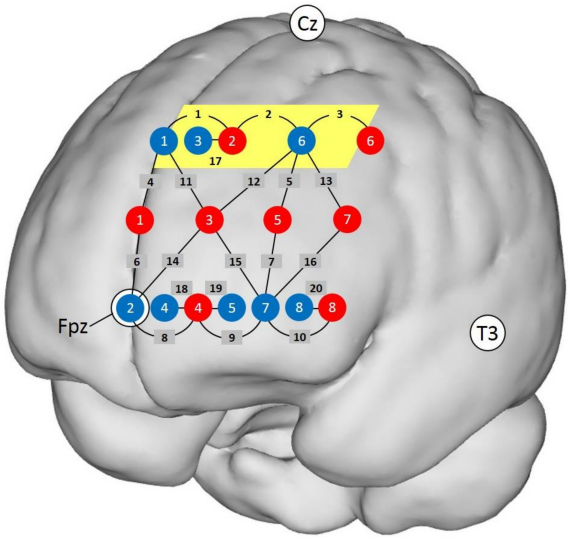

Figure 2. Location of the 20 channels projected on a standard brain. There were eight emitters (red dots) and eight detectors (blue dots). Black numbers indicate channels. The region of interest (ROI) is located in the area of Channels 1, 2 and 3 (highlighted in yellow). Channels 1–10 have a source-detector distance of ~30 mm; Channels 11–16, ~42 mm; Channels 17–20, ~15 mm. Detector 2 was placed at Fpz; Source 1 and Detector 1 on an imaginary line towards Cz; and the bottom row of fibers on an imaginary line towards T3.

Twenty channels were recorded at three wavelengths (780 nm, 805 nm and 830 nm), and the optical densities obtained from the FOIRE-3000 resulted in 60 time series. The $\log_{10}$-based optical density data were converted to natural logarithm-based absorbances, and each channel was referenced to the mean of each complete time series (~12 min duration). The absorbance data were then low-pass filtered to approximately 0.66 Hz using a moving average with a window length corresponding to 1.5 s. All 60 time series were smoothed separately. The concentration changes of O_2Hb and HHb were calculated with the modified Beer–Lambert law at the following wavelengths: λ_1 = 780 nm, λ_2 = 805 nm and λ_3 = 830 nm [48]. Time series of the concentration changes in O_2Hb and HHb were obtained for each channel separately. For the calculation, we used the molar absorption coefficients of Prahl [49] and the differential path length factor that was calculated from a generalizing equation [50].

To remove movement artifacts, the movement artifact removal algorithm (MARA) was employed [51]. The parameters for MARA, including the moving average window length L, threshold T and reconstruction parameter p, were individually selected for each channel and O_2Hb and HHb signal. We used a slightly different version of MARA, which did not use spline interpolation, but rather smoothed a running 2nd order least squares polynomial model (with p being the moving average window length) for the artifacts and subtracting this fit to preserve the high frequency information [52]. The parameter p was always set to seven samples, which corresponded to the preservation of the artifact data above approximately 1 Hz. The movement artifact removal was done in the following three steps: (1) trained raters analyzed the data; (2) experienced MARA users verified the results of the first step; and (3) a senior fNIRS data processing expert verified the cases marked as ambiguous. After the data were passed to MARA, they were again low-pass filtered (cut-off frequency, 0.2 Hz) with a 2nd order Chebyshev infinite-impulse-response filter.

To calculate the block response, a general linear model (GLM) was applied. We used a set of 129 Gaussian base functions with a standard deviation of 0.5 s that were separated by 0.5 s. The 129 base functions covered a time range of 65 s. The tasks were analyzed within a time window ranging from 5–45 s. The preceding 5 s were defined as the baseline, which was subtracted from the signal. The GLM followed the description in Gagnon et al. [47]. We excluded blocks from the GLM when the percentage of correct responses was less than 80% and 50% for the control and experimental conditions, respectively. Participants with less than three remaining blocks within each condition were excluded from further analyses. The remaining blocks were averaged by the GLM model, and a block average (subject-specific hemodynamic response function) was obtained for each variable (O_2Hb and HHb), subject and task. To reduce the amount of data for statistical analysis, the sampling frequency was reduced to 0.2 Hz after averaging 5 s-long segments. For the statistical analysis, the mean concentration changes in O_2Hb and HHb relative to baseline were calculated separately for each participant in both tasks (WM and DD), both conditions (control and experimental) and each channel (Channels 1–16). All statistical analyses were conducted with R [53]. To adjust for multiple testing, the Bonferroni–Holm correction [54] was applied for post hoc pairwise comparisons.

2.4. Time Course of the Study

In the first test session, over 250 participants were screened for mental ability. The participants who qualified for either the LA or HA mental ability group performed the DD task and visuospatial WM task in the second session. The order of the tasks was counterbalanced across the participants. The fNIRS measurements were performed in the third session. The average interval between the sessions was two weeks.

3. Results

3.1. Behavioral Data

Table 1 shows the descriptive statistics of the performance measures obtained in the visuospatial WM and DD tasks for the total sample, as well as the LA and HA groups. In the WM task,

the participants reached a mean ± standard deviation percentage of correct responses of 99.0 ± 2.4% in the control condition and 88.7 ± 7.2% in the experimental condition ($t(42) = -9.42$, $p < 0.001$, $d = -1.95$). In the DD task, the mean ± standard deviation percentage of correct responses was 94.6 ± 2.9% in the control condition and 78.0 ± 9.8% in the experimental condition ($t(42) = -10.08$, $p < 0.001$, $d = -2.30$). These findings clearly indicated that the task demands were significantly increased in the experimental condition compared with the control condition in both tasks. Furthermore, the percentages of correct responses did not differ significantly between the LA and HA groups in either task (see Table 2). Thus, we accomplished our goal of obtaining equivalent levels of subjective task difficulty for the participants in the two mental ability groups.

Table 1. Mean (M) and standard deviation (SD) of visual-spatial working memory span (WM) and duration discrimination threshold (DD) for the total sample (total, $n = 43$) as well as for the lower (LA, $n = 21$) and higher (HA, $n = 22$) mental ability groups.

Task	Total		LA		HA	
	M	**SD**	**M**	**SD**	**M**	**SD**
WM (span)	5.9	0.96	5.4	0.75	6.4	0.91
DD (threshold in ms)	28.7	10.61	30.2	11.15	27.3	10.11

Table 2. Mean (M) and standard deviation (SD) of percentages of correct responses in the working memory (WM) and duration discrimination (DD) tasks and both fNIRS conditions (experimental and control) for the total sample (total, $n = 43$) as well as for the lower (LA, $n = 21$) and higher mental ability (HA, $n = 22$) groups separately. *t*-tests and effect size estimates (Cohen's *d*) comparing the two groups.

Task	Condition	Total		LA		HA				
		M	**SD**	**M**	**SD**	**M**	**SD**	***t*(41)**	***p***	***d***
WM	control	99.0	2.38	99.1	2.23	98.9	2.56	0.25	0.804	0.08
	experimental	88.7	7.15	89.0	7.22	88.4	7.23	0.27	0.791	0.08
DD	control	94.6	2.85	94.5	2.86	94.7	2.91	−0.28	0.783	−0.09
	experimental	78.0	9.84	79.0	9.98	77.1	9.85	0.63	0.530	0.19

3.2. fNIRS Data

Definition of the region of interest (ROI): We applied an exploratory and data-driven approach to investigate possible ROIs [55]. We first selected channels with which we could observe the typical patterns of hemodynamic responses during functional activation (increase in O_2Hb and decrease in HHb) [41]. For the frontal cortex, this pattern enhances the probability that the signal does not contain systemic changes [41,56] and indicates good signal quality [57]. We therefore selected only the channels in which O_2Hb and HHb were negatively correlated in both conditions (control and experimental) and both tasks (WM and DD). We applied this criterion to both tasks to ensure that any effects would be detected with the highest probability. This criterion was met by Channels 1, 2 and 3. Plots of the time course of O_2Hb and HHb for all three channels, both conditions (active control and experimental) and both tasks (WM and DD) can be found in the Supplementary Materials (Figure S2). All three channels were located next to each other in a region covering Brodmann Area (BA) 8, and thus, they defined our ROI. The Montreal Neurological Institute coordinates (x, y, and z) of Channels 1–3 were (−8, 49, 47), (−26, 43, 47) and (−40, 25, 47), respectively. The mean concentration changes in O_2Hb and HHb relative to baseline of Channels 1–3 were averaged and provided the value for our ROI. Within this ROI, the negative correlations between O_2Hb and HHb were significant for both tasks and both conditions ($r_{WM\ control} = -0.56$, $r_{WM\ experimental} = -0.75$, $r_{DD\ control} = -0.74$, $r_{DD\ experimental} = -0.78$ (all ps < 0.001, two-tailed)). A projection of the ROI on a standard brain is depicted in Figure 2.

To examine whether the changes in functional activation observed during the performance of the WM task were specific for WM-related processes and not related to more general subsidiary processes,

we investigated the differences in the Hb oxygenation concentration changes observed in the control and experimental conditions in the WM task by conducting a two-way analysis of variance with the within-subject factors of Hb oxygenation (O_2Hb and HHb) and condition (control and experimental). This analysis yielded no significant main effects (Hb oxygenation, $F(1, 42) = 2.84$, $p = 0.099$, $\eta_p^2 = 0.063$; condition, $F(1, 42) = 0.01$, $p = 0.920$, $\eta_p^2 < 0.001$). Instead, a significant interaction of Hb oxygenation and condition was found ($F(1, 42) = 4.41$, $p = 0.042$, $\eta_p^2 = 0.095$). Post hoc pairwise comparisons revealed a significant decrease in the relative concentration of HHb in the experimental condition compared to the control condition ($t(42) = 3.82$, $p = 0.002$, $d = 0.59$). In addition, the O_2Hb relative concentration was significantly increased compared to the HHb relative concentration ($t(42) = 2.61$, $p = 0.037$, $d = 0.70$) in the experimental condition (see Figure 3 and Table 3).

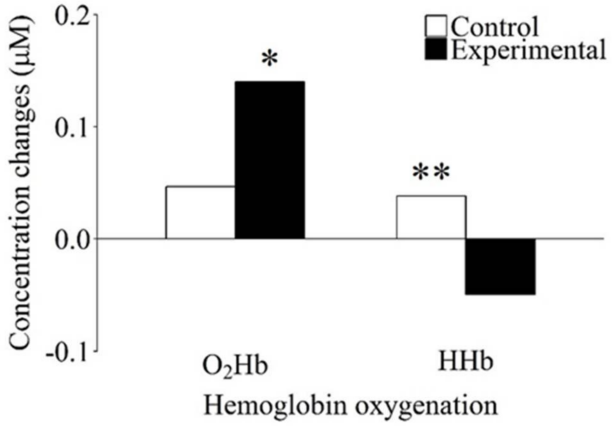

Figure 3. Differences in concentration changes for oxygenated (O_2Hb) and deoxygenated (HHb) hemoglobin as a function of condition for the working memory task. HHb concentration was significantly lower in the experimental than in the control condition. Within the experimental condition, there was a significant difference in concentration change between O_2Hb and HHb. * significantly different from HHb concentration change in the experimental condition ($p < 0.05$); ** significantly different from HHb concentration change in the experimental condition ($p < 0.01$).

Table 3. Mean (M) and standard deviation (SD) of oxygenated (O_2Hb) and deoxygenated (HHb) hemoglobin concentration changes as a function of fNIRS condition (control and experimental) in the working memory (WM) and duration discrimination (DD) tasks for the total sample (Total, $n = 43$), as well as for the lower (LA, $n = 21$) and higher (HA, $n = 22$) mental ability groups.

Task	Hemoglobin Oxygenation	Condition	Total		LA		HA	
			M	SD	M	SD	M	SD
WM	O_2Hb	control	0.05	0.38	−0.07	0.35	0.15	0.39
		experimental	0.14	0.35	0.18	0.39	0.09	0.31
	HHb	control	0.04	0.14	0.08	0.16	0.00	0.12
		experimental	−0.05	0.15	−0.07	0.15	−0.03	0.16
DD	O_2Hb	control	0.14	0.48	0.10	0.35	0.17	0.59
		experimental	0.11	0.47	0.07	0.35	0.14	0.57
	HHb	control	−0.03	0.16	−0.01	0.14	−0.05	0.18
		experimental	−0.03	0.19	−0.02	0.10	−0.04	0.25

To confirm whether the increased functional activation observed in the experimental condition represented WM task-specific processes and not general effects of increased task demands, we evaluated whether the differences in the O_2Hb and HHb concentration changes that occurred as a function of fNIRS condition would also be observed in the DD task. For this purpose, a two-way

analysis of variance that was identical to the one applied for the visuospatial WM task was conducted. This analysis did not yield any indication of concentration changes in Hb oxygenation. Neither the main effects of Hb oxygenation ($F(1, 42) = 3.14$, $p = 0.084$, $\eta_p^2 = 0.070$) or condition ($F(1, 42) = 0.57$, $p = 0.453$, $\eta_p^2 = 0.013$), nor the interaction of these factors ($F(1, 42) = 0.11$, $p = 0.743$, $\eta_p^2 = 0.003$) was statistically significant (see Figure 4 and Table 3).

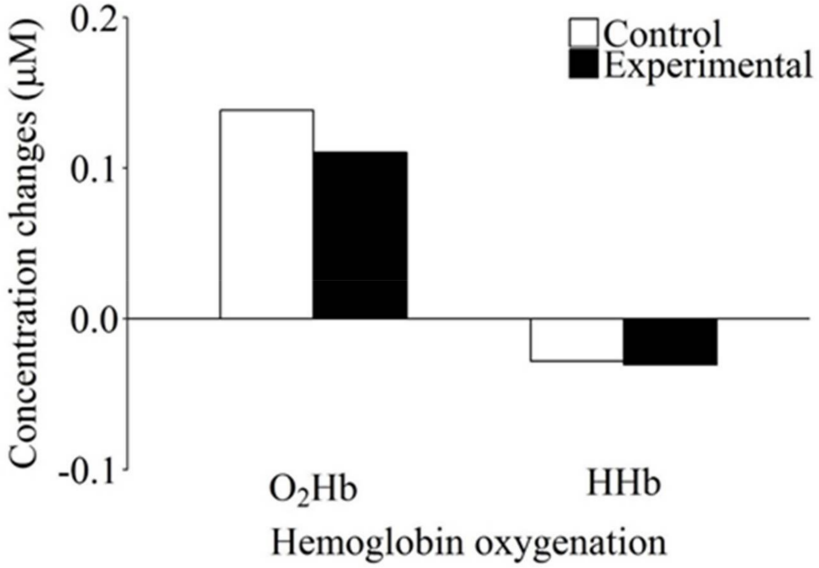

Figure 4. Concentration changes for oxygenated (O_2Hb) and deoxygenated (HHb) hemoglobin as a function of condition for the duration discrimination task. Neither O_2Hb nor HHb showed a significant difference in hemoglobin oxygenation concentration change between the control and the experimental condition.

As a final step, we examined if mental ability level effectively moderated the concentration changes in Hb oxygenation observed in the WM task. For this purpose, a three-way analysis of variance with Hb oxygenation (O_2Hb and HHb) and condition (experimental and control) as the two within-subject factors and mental ability (LA and HA) as the between-subjects factor was performed. This analysis yielded no significant main effects of Hb oxygenation ($F(1, 41) = 2.75$, $p = 0.105$, $\eta_p^2 = 0.063$), condition ($F(1, 41) = 0.21$, $p = 0.884$, $\eta_p^2 = 0.001$) or mental ability ($F(1, 41) = 0.49$, $p = 0.486$, $\eta_p^2 = 0.012$). However, a significant interaction of Hb oxygenation and condition ($F(1, 41) = 5.33$, $p = 0.026$, $\eta_p^2 = 0.115$), as well as a statistically significant three-way interaction of all combined factors ($F(1, 41) = 7.14$, $p = 0.011$, $\eta_p^2 = 0.148$) was observed. No significant two-way interactions were found for condition and mental ability ($F(1, 41) = 3.32$, $p = 0.076$, $\eta_p^2 = 0.075$) or Hb oxygenation and mental ability ($F(1, 41) = 0.48$, $p = 0.492$, $\eta_p^2 = 0.012$).

To better assess the significant three-way interaction, two separate two-way analyses of variance were conducted with the factors of Hb oxygenation and condition for the LA and HA groups. For the LA group, no significant main effects of Hb oxygenation ($F(1, 20) = 0.36$, $p = 0.555$, $\eta_p^2 = 0.018$) or condition ($F(1, 20) = 2.62$, $p = 0.121$, $\eta_p^2 = 0.116$) were revealed, whereas the interaction between these two factors was significant ($F(1, 20) = 16.67$, $p = 0.001$, $\eta_p^2 = 0.455$). The post-hoc pairwise comparisons indicated that the relative concentration of O_2Hb was significantly higher in the experimental condition than in the control condition ($t(20) = 3.30$, $p = 0.039$, $d = 0.68$). A difference was observed in the opposite direction for HHb: the relative HHb concentration was significantly lower in the experimental condition than in the control condition ($t(20) = 4.93$, $p < 0.001$, $d = 0.97$ (see Figure 5A)). In contrast to the LA group, neither a statistically significant main effect of Hb oxygenation ($F(1, 21) = 3.79$, $p = 0.065$, $\eta_p^2 = 0.153$) or condition ($F(1, 21) = 1.14$, $p = 0.298$, $\eta_p^2 = 0.51$), nor a statistically significant

interaction between these two factors ($F(1, 21) = 0.54$, $p = 0.819$, $\eta_p^2 = 0.003$) was found for the HA group (see Figure 5B).

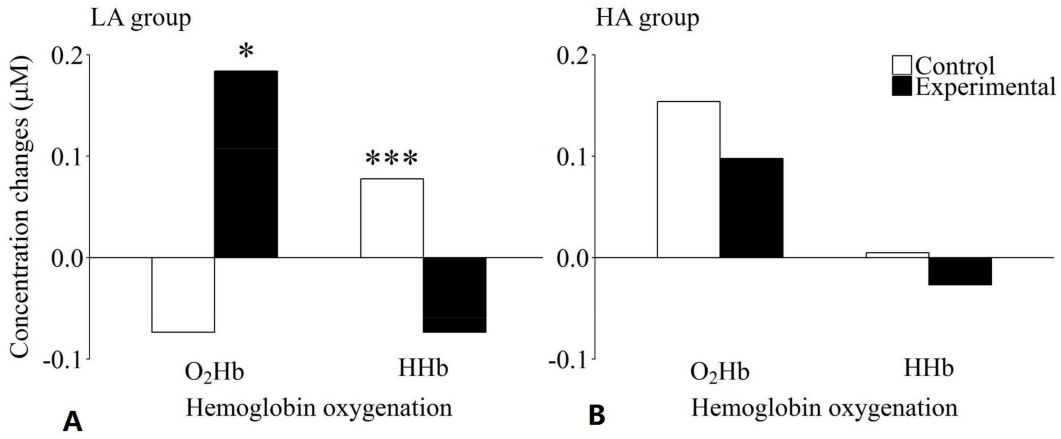

Figure 5. Effects of level of mental ability and condition on hemoglobin oxygenation concentration changes for the working memory task in the lower (**A**) and the higher (**B**) mental ability group. The lower mental ability group showed significantly increased O_2Hb and significantly decreased HHb concentrations in the experimental compared to the control condition. No significant differences could be observed for the higher mental ability group. * Significantly different from O_2Hb concentration change in the control condition ($p < 0.05$); *** significantly different from HHb concentration change in the experimental condition ($p < 0.001$).

4. Discussion

The present study investigated whether fNIRS was useful for measuring WM-specific process-induced functional activation in the prefrontal cortex that was independent of competing processes that were less specific to WM functioning. In particular, we examined whether the differences in Hb oxygenation concentration changes observed during the performance of the WM task were due to specific WM capacity-related processes rather than to subsidiary processes, such as motor processes or perceptual encoding (e.g., [58,59]), or more general processes, such as those related to increased task demand. To achieve this goal, we compared the Hb oxygenation concentration changes that were observed during task performance in the experimental condition with those observed during the active control condition in both a WM and a DD task.

Initially, an ROI was identified. Only three out of the 16 channels met our strict criterion of a negative correlation between O_2Hb and HHb in the experimental and control conditions of both tasks. These three channels defined our ROI above BA 8 in the left hemisphere. While Channels 1 and 2 covered the left superior frontal gyrus, Channel 3 was located above the left middle frontal gyrus. Despite the limited size of our holder, the data-driven approach for defining our ROI resulted in an area that has been shown to be relevant for visuospatial WM functioning in previous studies. For example, Boisgueheneuc et al. [60] have reported that patients with a lesion in BA 8 exhibit WM deficits, especially in visuospatial tasks, compared to patients with lesions that did not involve the superior frontal gyrus and healthy controls. However, not only different WM task modalities (e.g., visuospatial and verbal), but also distinct WM processes (e.g., encoding, storing and retrieval of information) are represented by different functional activation patterns in the brain. For example, these functional activation patterns differ depending on whether the localization or identity of a stimulus needs to be memorized or whether the stimulus must be reproduced on retrieval or simply verified. Rottschy et al. [11] have shown that memory for stimulus location and the reproduction of a memorized stimulus lead to increased functional activation in the posterior superior frontal gyrus. This finding is consistent with the outcomes of the present study in which the WM task also required the storing and subsequent

reproduction of the localization of black squares that was accompanied by functional activation in BA 8.

In order to more clearly attribute the functional activation observed during the processing of the WM task to task-specific processes, we compared an active control condition that required only general subsidiary processes with an experimental condition that additionally required WM-specific processes. In the experimental condition, O_2Hb increased and HHb decreased, which corresponds to the typical pattern of hemodynamic responses observed during functional activation [41,61]. Comparison of the conditions clearly indicated additional resource consumption by the WM-specific task demands in the experimental condition.

This finding was in line with the outcomes of previous fNIRS studies that applied multiple levels of task difficulty. For example, Causse and colleagues [62] investigated changes in O_2Hb and HHb in the prefrontal cortex as a function of task difficulty in the spatial WM task in the Cambridge Neuropsychological Test Automated Battery. Their results revealed that fNIRS was sensitive to variations in task difficulty as O_2Hb increased and HHb decreased with the increasing number of localizations that needed to be memorized. Similar patterns of O_2Hb and HHb changes have been reported by several other studies applying verbal n-back tasks with letters as stimuli. The task demands were experimentally varied by using either 1-, 2- or 3-back [8,9,63] or 0-, 1-, 2- or 3-back conditions [64,65]. These studies also confirmed that increasing task difficulty resulted in increased O_2Hb and decreased HHb concentrations.

Despite these consistent findings for task difficulty, it remains unclear whether this typical functional activation pattern is caused by WM-specific processes or is due to the higher degree of task demand caused by the more difficult conditions and is independent of the specific task under investigation. In order to confirm whether the increased functional activation observed in the experimental condition in the present study was caused by WM task-specific processes and did not reflect a general effect of a task-independent increase in task demand, we implemented DD as a supplementary task that was functionally independent of WM capacity. DD of extremely brief intervals in the range of milliseconds is processed subcortically [25,29] and should, therefore, not cause any changes in prefrontal O_2Hb and HHb. If the differences in Hb oxygenation between the control and experimental conditions that were detected with the WM task were predominantly task-unspecific, thus indicating that the changes caused by the experimentally-induced increase in general task demand would be produced by any given task, a similar pattern should be observed in the differences in Hb oxygenation in both the WM and DD tasks. If, however, the Hb oxygenation differences were only observed during the processing of the WM task and not during the performance of the DD task, the measured differences in the concentration changes might be directly related to WM capacity. The complete absence of any changes in O_2Hb and HHb in the experimental and control conditions in the DD task clearly indicated that the pattern of changes observed with the WM task reflected a hemodynamic response that was highly specific to the experimentally-increased visuospatial WM capacity-related task demands. Thus, to the best of our knowledge, the present study is the first to provide direct evidence of the sensitivity of fNIRS for identifying hemodynamic responses specific for visuospatial WM capacity by utilizing a WM-unrelated control task.

Comparisons between different types of tasks (e.g., WM and DD) and different task conditions (e.g., active control and experimental) are only conclusive if prerequisites were created that enabled their comparison. We accomplished this by developing a control and experimental condition for each task and applying an adaptive experimental approach in both tasks. The goal was to keep the items in the control condition in both tasks as simple as possible so that no specific task demands were required. At the behavioral level, this was evident because virtually all items were correctly solved by all participants. In contrast, the items in the experimental conditions in the WM and DD tasks should contain additional specific task demands. The specific task demands of the WM and DD tasks rendered the experimental condition in both tasks more difficult than the respective control conditions.

In both tasks, the percentage of correct answers in the control condition was significantly higher than that in the experimental condition.

With the adaptive approach, we established that all individuals were presented with task demands that were subjectively equally difficult in both tasks. At the behavioral level, this was demonstrated because the two mental ability groups did not differ in the percentages of correct responses in both types of tasks and both task conditions. With 78% correct responses, the DD task was somewhat more difficult than the WM task, which had 89% correct responses. This should have facilitated the occurrence of a general effect of a task-independent increase in task demand in the DD compared to the WM task. Based on these considerations, the complete lack of any changes in Hb oxygenation in the experimental condition in the DD task could not be attributed to the task demand level being too low to elicit a hemodynamic response relative to the WM task.

In the final step, the potential moderating effects of individual differences in mental ability on the observed WM-specific changes of Hb oxygenation were investigated. For this purpose, we compared the WM-specific changes in Hb oxygenation in the LA and HA groups. It should be noted that our LA group consisted of individuals with an average mental ability (IQ ranging from 90–112), while our HA group comprised individuals who were considerably above average mental ability (IQ ranging from 130–145). The analysis revealed a clear-cut moderating effect of mental ability level. In the LA group, the WM-specific task demands of the experimental condition induced the typical functional activation pattern, which was indicated by an O_2Hb increase and HHb decrease (e.g., [41,61,66]). This pattern of hemodynamic changes was indicative of functional activation in the experimental condition compared to the control condition. In contrast, the HA group showed an almost identical pattern of Hb concentration changes in both the control and experimental conditions without any indication of functional activation.

These Hb oxygenation patterns that differed as a function of individual level of mental ability were in line with the results of various neuroimaging studies. Early PET and single-photon emission computed tomography studies investigating the link between mental ability and functional activation have reported less functional activation in individuals with higher mental abilities during the processing of cognitive tasks compared with individuals with lower mental abilities (e.g., [32,67,68]). Subsequent fMRI studies further differentiated these findings by systematically varying task demand [69–73]. These studies revealed that the described effects occurred, especially with tasks with low to medium difficulties. More recently, this reciprocal action between cognitive task demand and level of mental ability on functional activation was confirmed by an fNIRS study [74]. When cognitive decision-making tasks were performed, low-conflict decisions (i.e., lower cognitive task demands) produced a stronger hemodynamic response in the frontal cortex in participants with low mental abilities compared with participants with high mental abilities. This pattern of functional activation, however, did not hold for high-conflict decisions with enhanced cognitive task demands.

Overall, the findings of these previous studies revealed that individuals with lower mental abilities showed stronger functional activation compared to individuals with higher mental abilities during the processing of cognitive tasks with low to moderate levels of task difficulty. At the same time, the performances on these cognitive tasks confirmed the differences between the groups: the individuals with lower mental abilities consistently performed more poorly than the individuals with higher mental abilities did during the processing of the same WM task. This latter finding clearly indicated that a given cognitive task with low difficulty was subjectively more demanding for individuals with lower mental abilities compared to individuals with higher mental abilities. Thus, it is reasonable to assume that this inequality in subjective task demand may have caused the observed differences in functional activation between the low and high mental ability groups.

Taking this background into account, it appeared reasonable to assume that the observed differences in functional activation would disappear when the participants were required to process a cognitive task with the same level of subjective task demand. In order to ensure that all individuals experienced an equivalent level of subjective task demand, we applied an adaptive approach in the

present study. With this experimental approach, we ensured that each participant was presented with the same visuospatial WM task with task difficulty individually adjusted to obtain a virtually-identical level of subjective task demand irrespective of his/her individual level of mental ability.

As a result, both the LA and HA groups achieved correct responses on the order of 88%, which was indicative of a cognitive task of low difficulty. This low level of task difficulty corresponded to the difficulty level of the WM tasks used in the previous studies, in which a differential effect in functional activation was demonstrated between the mental ability groups. Rather unexpectedly, however, we found that the difference in functional activation still existed despite the virtually identical subjective task demands for both mental ability groups. Therefore, it must be ruled out that the observed differences in functional activation between the LA and HA groups were caused by differences in subjective task demands, as has been suggested by the results of previous studies. Rather, individuals with lower mental abilities seem to utilize more cortical oxygen compared with high ability individuals while solving an easy visuospatial WM task that was subjectively adjusted for cognitive task demand across subjects. This highly surprising finding may indicate that qualitatively different cognitive processes were adopted by the LA and HA individuals to solve the task.

In order to provide converging evidence of the validity of this finding, additional samples of LA and HA participants should be tested in future studies. Furthermore, additional studies are required to examine whether a similar moderating effect of mental ability on functional activation can also be demonstrated for other WM tasks.

5. Conclusions

Taken together, our findings clearly indicated that that hemodynamic responses recorded by fNIRS were sensitive to visuospatial WM capacity-related processes. Furthermore, the functional activation observed proved to be specific to the WM processes under investigation rather than to general effects of increased task demand. Finally, we provided converging evidence for a moderating effect of the individual level of mental ability on the hemodynamic responses. Because this effect could not be attributed to differences in subjective task demand, our findings suggest that qualitatively different processes were involved in visuospatial WM processing in LA and HA individuals.

Supplementary Materials: The following are available online at http://www.mdpi.com/2076-3425/8/4/62/s1: Figure S1: Image of probe holder mounted on the left forehead, Figure S2: Grand averages and confidence intervals of evoked hemodynamic concentration changes across all subjects for Channels (CH) 1–3. Red line = oxygenated hemoglobin, blue line = deoxygenated hemoglobin, each with the 95% confidence interval.

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Functional Near-Infrared Spectroscopy Recordings of Visuospatial Working Memory Processes. Part II: A Replication Study in Children on Sensitivity and Mental-Ability-Induced Differences in Functional Activation

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Abstract: In a previous study in young adults, we showed that hemodynamic changes as measured by functional near-infrared spectroscopy (fNIRS) were sensitive for identifying visuospatial working memory (WM)-related functional brain activation in the prefrontal cortex. This functional activation, however, could not be verified for participants with far-above-average mental ability, suggesting different cognitive processes adopted by this group. The present study was designed to confirm these findings in 11- to 13-year-old children by applying the same study design, experimental task, fNIRS setup, and statistical approach. We successfully replicated the earlier findings on sensitivity of fNIRS with regard to visuospatial WM-specific task demands in our children sample. Likewise, mental-ability-induced differences in functional activation were even more pronounced in the children compared with in the young adults. By testing a children sample, we were able to not only replicate our previous findings based on adult participants but also generalize the validity of these findings to children. This latter aspect seems to be of particular significance considering the relatively large number of fNIRS studies on WM performance in children.

Keywords: fNIRS; visuospatial working memory processing; children; sensitivity; subjective task demand; mental ability; replication; generalization

1. Introduction

More than 20 years ago, the noninvasive and continuous measurement of brain activation with functional near-infrared spectroscopy (fNIRS) was introduced (e.g., [1,2]). A major advantage of fNIRS over other neuroimaging techniques such as positron emission tomography (PET) and functional magnetic resonance imaging (fMRI) is its compact measurement system [3] that puts less strain on participants. Moreover, it is less sensitive to motion artifacts [3], which enables its use in a variety of experimental settings [4]. With fNIRS, functional brain activation is measured noninvasively [5] by recording changes in oxygenated and deoxygenated hemoglobin (Hb) concentrations. The typical pattern of the hemodynamic response during functional brain activation is an increase in oxygenated hemoglobin (O_2Hb) and a concomitant decrease in deoxygenated hemoglobin (HHb) [6]. As a consequence, the two signals are negatively correlated during functional activation [7–9]. Commonly, the concentration change of HHb is noticeably smaller than that of O_2Hb [10,11].

Due to the advantages mentioned above, fNIRS has been increasingly used in cognitive research [12]. Several studies have assessed mental workload with verbal working memory (WM) tasks of varying load conditions and confirmed that increasing task difficulty resulted in increased O_2Hb and decreased HHb concentrations [13–17]. The same pattern of Hb concentration changes could also be shown for visuospatial WM tasks (e.g., [18]). Validation studies using simultaneous fNIRS and fMRI measurements revealed a high correlation between the fNIRS-Hb and fMRI-blood oxygen-level dependent (BOLD) signals in motor tasks [19–24] as well as in WM tasks [22,25,26].

An alternative approach for validating the usefulness of fNIRS in WM research aims at providing evidence for the sensitivity of the fNIRS signal with regard to WM-specific task demands. More specifically, sensitivity refers to the question of whether the fNIRS technology is able to dissociate task-specific from more general task-unspecific processes. In order to pin down task-specific processes, an active control condition can be implemented where most of the perceptual and response-related processes are identical to those in the experimental condition whereas the task-specific processes of interest are only required for the experimental task. Differences in functional activation between the active control and experimental condition can then be attributed to the task-specific functional activation. This approach of validation, which is not based on a comparison with another method but on a variation of the task design, was realized in a first study by Witmer et al. [27]. In this study, the functional activation in Brodmann area (BA) 8 during the processing of a visuospatial WM task was investigated. BA 8, including the superior frontal gyrus, has been shown to be crucial for visuospatial WM processing (cf. Witmer et al. [27]). For example, in a lesion study by du Boisgueheneuc et al. [28], patients with lesions in the superior frontal gyrus, especially of the left hemisphere, showed deficits in visuospatial WM tasks. Similarly, a meta-analysis by Rottschy et al. [29] also confirmed that memory of stimulus location and the reproduction of a memorized stimulus lead to an increased functional activation in the left superior frontal gyrus.

Witmer et al.'s [27] sample consisted of young adults, 22 female and 21 male, ranging in age from 18 to 24 years. In the active control condition, there was no indication of a significant difference between O_2Hb and HHb concentration changes. In the experimental condition, however, a statistically significant difference between O_2Hb and HHb concentration changes occurred due to an increase in O_2Hb and a simultaneous decrease in HHb concentration. This opposite effect on O_2Hb and HHb concentration changes clearly corresponds to the typical hemodynamic response pattern observed during functional activation [6,30].

The primary goal of the present study was to investigate whether this effect was a one-time result or whether it can be replicated, and whether it occurs in other samples of participants. The necessity to replicate significant study results is strongly encouraged by the current debate referred to as the replication crisis (e.g., [31–33]). By applying the same study design, experimental task, fNIRS setup, and statistical approach as in our previous study [27], the current study conforms to a major requirement of good research practices derived from the replication crisis (e.g., [34]).

In order to critically evaluate the replicability and sample independence of Witmer et al.'s [27] results, a sample of children was examined in the present study. The fNIRS method is very well suited for measurements in children. Scalp–brain distances affect the photon path and have a direct impact on fNIRS data quality as indicated by the noise level in the data [26]. As the scalp–brain distance at the forehead is substantially shorter in children than in adults, measurements of children provide a better signal-to-noise ratio and, thus, a clearer fNIRS signal compared with adults [26,35,36].

Several studies pointed out that the pattern of functional activation during cognitive processing varies among individuals with different levels of mental ability. Early neuroimaging studies using single-photon emission computed tomography (SPECT) and PET reported less functional activation during the processing of cognitive tasks in individuals with higher mental ability compared with in individuals with lower mental ability (e.g., [37–39]). More recent fMRI studies provided converging evidence that this differential effect arises in particular when cognitive tasks with low to medium levels of task difficulty were used [40–44].

Such a mutual interference between level of mental ability and cognitive task demand on functional activation was recently confirmed by an fNIRS study using low- and high-conflict decision-making tasks [45]. While low-conflict decisions, involving lower cognitive task demands, produced a weaker hemodynamic response in the frontal cortex of participants with higher mental ability compared with in participants with lower mental ability, this pattern of functional activation did not occur in high-conflict decisions with enhanced cognitive task demands.

Overall, these studies suggested that individuals with lower mental ability (LA) show stronger functional activation compared with individuals with higher mental ability (HA) during the processing of a given cognitive task with low to moderate levels of task difficulty. At the same time, however, LA individuals performed more poorly than HA individuals [38,41–45]. This latter finding indicates that the same cognitive task with a low to moderate level of task difficulty was subjectively more demanding for LA than for HA individuals. Therefore, it appears reasonable to assume that the observed differences in functional brain activation were caused by the unequal subjective task demands experienced by LA and HA participants. These differences should thus disappear when participants perform a cognitive task controlled for the level of subjective task demand.

This issue was also addressed in Witmer et al.'s [27] study. In order to assess whether there is a moderating effect of mental ability on functional activation, participants were selected in a way that allowed assigning them to a LA or a HA group. Participants' mental ability was assessed by Cattell's Culture Fair Test 20-R [46]. To prevent an overlap in the 95% confidence interval between the two groups, only participants with IQ scores ranging from 90 to 112 (LA group) and from 130 to 145 (HA group) were included in the study. By applying an adaptive approach, Witmer et al. [27] ensured that all participants performed the same visuospatial WM task with task difficulty individually adjusted to obtain an equivalent level of subjective task demand irrespective of the participant's individual level of mental ability. Hence, if the stronger functional activation in the LA group compared with in the HA group described in previous studies was due to higher subjective task demands, we would no longer expect differences, as the subjective task difficulty was comparable for both groups.

Despite the virtually identical subjective task demands for all participants in Witmer et al.'s [27] study, the difference in functional brain activation between the LA and HA group was still present. In the LA group, the WM-specific task demands of the experimental condition yielded the typical pattern of functional activation as indicated by an O_2Hb increase and a concomitant HHb decrease. The HA group, on the contrary, displayed an almost identical pattern of Hb concentration changes in both the active control and experimental condition without any indication of functional activation. This finding clearly argues against the notion that the observed differences in functional brain activation originated from differences in subjective task demands. Rather, LA participants seemed to require more cortical oxygen compared with HA participants for solving an easy visuospatial WM task adjusted for subjective task demand.

Taken together, the major goal of the present study was to replicate the finding that fNIRS is sufficiently sensitive to measure visuospatial WM-specific processes. As an indication of sufficient sensitivity of fNIRS regarding visuospatial WM-specific processes, we predicted that the two-way interaction between Hb oxygenation and task condition would become significant. In particular, we expected a more pronounced functional activation, as indicated by the typical pattern of an increase in O_2Hb and a simultaneous decrease in HHb, during the experimental condition compared with during the active control condition. The second goal of the present study was to reproduce the moderating effect of mental ability on functional activation. We expected significant differences in functional brain activation between the control and experimental condition in the LA but not in the HA group. In the LA group, the increase in O_2Hb and the simultaneous decrease in HHb should be substantially more pronounced in the experimental compared to the active control condition. For the HA group, we did not expect any functional activation in either of the two task conditions. At the statistical level, this pattern should become evident from a significant three-way interaction between Hb oxygenation, task condition, and mental ability.

2. Materials and Methods

2.1. Participants

More than 250 children ranging in age from 11 to 13 years were recruited from public schools and screened for mental ability. In order to determine two mental ability groups whose 95% confidence intervals did not overlap, only children with an intelligence quotient (IQ) lower than or equal to 96 and higher than or equal to 115 were selected for the present study. This procedure resulted in a lower-ability (LA) group with IQ scores ranging from 72 to 96 (mean IQ score ± standard deviation: 89 ± 7.17) and a higher-ability (HA) group with IQ scores ranging from 115 to 141 (mean IQ score ± standard deviation: 122 ± 7.88). The LA group consisted of eight boys and ten girls (mean age: 11.6 ± 0.61 years), and the HA group consisted of 12 boys and 12 girls (mean age: 11.8 ± 0.59 years).

All participants were right-handed, and caregivers reported normal hearing and normal or corrected-to-normal vision. Based on a health questionnaire filled in by the caregiver of each child, all children were healthy with no history of psychiatric or neurological illness, serious head injury, or medication intake. The caregiver of each participating child provided written informed consent after being given detailed information on the study protocol and the NIRS recording procedure. In addition, the children gave oral consent. The study was conducted in accordance with the Declaration of Helsinki and the study protocol was approved by the ethics committee of the Faculty of Human Sciences of the University of Bern (Bern, Switzerland) (date of approval: 29 July 2014; project identification code: No. 2014-6-880651).

2.2. Assessment of Psychometric Intelligence

Mental ability was assessed by the short version of the German adaptation of Cattell's Culture Fair Intelligence Test (CFT 20-R; [46]). The CFT 20-R is a nonverbal test that consists of four different inductive reasoning subtests and can be considered an estimate of an individual's general fluid intelligence [46,47]. The time allowed was 4 min for Subscales 1 and 2 and 3 min for Subscales 3 and 4. As a measure of mental ability, the number of correctly solved items was transformed into an IQ score. The CFT 20-R manual provides IQ norms for test takers ranging in age from 8.5 to 60 years.

2.3. Quantification of Individual Visuospatial WM Spans

A combined version of the Patterns–Memory Task [48] and the Matrix Task [49] was used to quantify individual visuospatial WM spans. The task was computer-controlled and programmed with E-Prime experimental software (Psychology Software Tools, Inc., Sharpsburg, PA, USA). Each trial started with the presentation of a fixation cross for 500 ms, followed by a black 4 × 4 grid (13.2 × 13.2 cm) consisting of 16 white squares, referred to as the empty grid, presented in the center of a touchscreen monitor. The viewing distance was about 60 cm and sufficiently close to the child to comfortably reach the touchscreen monitor without body movement.

The task started with a block of four trials with a set of two squares to be memorized. More precisely, two of the 16 squares successively turned black for 1000 ms. Participants were instructed to memorize the order of appearance and the location of the black squares. Next, a question mark was displayed for 1000 ms, followed by the empty grid that was used as an input template for the participant's response. The participant was prompted to touch, in reverse order, those two squares on the empty grid that previously turned black. The second block comprised four trials with a set of three squares to be memorized, the third block comprised four trials with a set of four squares to be memorized, and so on. Thus, if the participant was able to correctly solve at least three trials within a given block, the set of squares to be memorized was extended by one additional square in the next block. The number of squares of the last block in which this criterion had been met constituted the participant's visuospatial WM span. The black squares were presented in a pseudo-randomized order in all trials.

2.4. Experimental and Active Control Conditions of the fNIRS Study

The procedure and stimuli were identical to those in the ordinary WM task, with the exception that no adaptive procedure was applied. For the fNIRS recordings, an experimental condition, i.e., the visuospatial WM task, was contrasted with an active control condition. This enabled the application of the subtraction approach, which allows the identification of WM-specific changes in Hb oxygenation concentration [6,50,51].

In the experimental condition, visuospatial WM-specific processes as well as WM-unspecific processes, such as perceptual encoding of the stimuli, response selection, and execution of the motor response, were required. For each child, an individual level of task difficulty was chosen based on his/her WM span determined in the previous experimental session. For example, a child with an individual WM span of four items was presented with a series of four black squares that appeared successively in a pseudo-randomized order. The child was instructed to memorize the order of appearance and the location of the four black squares and subsequently prompted to touch, in reverse order, those four squares on the empty grid that previously turned black. With this procedure, subjective task demand was held constant for all children.

In the active control condition, the number of squares that turned black was identical to the experimental condition. Unlike in the experimental condition, however, the squares no longer turned black in a pseudo-randomized but in a systematic order (either from left to right or from top to bottom). As a result, the task demand on WM was extensively reduced in the active control compared to the experimental condition, whereas the task-unspecific processes were identical in both conditions.

Task instructions were given orally via headphones. Prior to the proper experiment, each child completed seven practice trials to refresh the WM task and to ensure that the task instructions were fully understood. The fNIRS measurement started with a 45 s resting phase, followed by the task conditions. The entire fNIRS visuospatial WM task consisted of four blocks of the active control condition and four blocks of the experimental condition. Both types of blocks were presented for 40 s each in alternating order. The order of the experimental and active control blocks was counterbalanced across participants. All blocks were separated from each other by a resting phase referred to as baseline block (see Figure 1). During the resting phase, children were instructed to sit quietly with their eyes open. To reduce the influence of Mayer waves, which are spontaneous oscillations in blood flow that affect the fNIRS signal [52], and to prevent influences of blood flow changes due to rhythmic changes, the duration of the resting phases was randomly varied from 25 to 40 s. As a behavioral measure, the respective percentages of correctly solved trials were determined for the experimental and the active control condition.

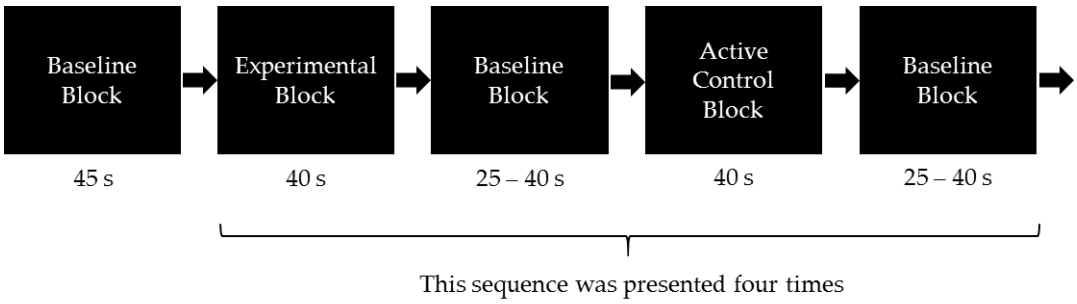

Figure 1. Illustration of the block design, which contained eight baseline blocks (resting phases), four experimental blocks, and four active control blocks. After the first baseline block, participants started either with an experimental or an active control block (order was counterbalanced across participants).

2.5. fNIRS Recordings

Functional near-infrared spectroscopy (fNIRS) data were acquired and preprocessed exactly the same way as in Witmer et al.'s [27] study. Briefly summarized, a multichannel system (FOIRE 3000,

Shimadzu Corporation, Kyoto, Japan) was used which recorded optical density changes from 20 channels (light source–light detector combinations) at three wavelengths (780 nm, 805 nm, 830 nm) and at three different distances (four channels at ~15 mm, 10 channels at ~30 mm, six channels at ~42 mm). The optical probe included an array of 16 light fibers connected to the fNIRS system (eight sources and eight detectors). The probe holder was placed over the left frontal scalp, between the 10–20 landmarks Fpz, Cz, and T3 (see Figure 2). Every light fiber position was measured in Montreal Neurological Institute (MNI) coordinates using a FASTRAK® 3D magnetic field digitizer (Polhemus, Colchester, VT, USA). O_2Hb and HHb relative concentration changes were calculated from the optical densities. The short channels (~15 mm) were used to regress out superficial influences [4,6] from the longer channels [53], but only if the correlation between the time series of the two signals was sufficient, such that $R^2 > 0.1$ [54].

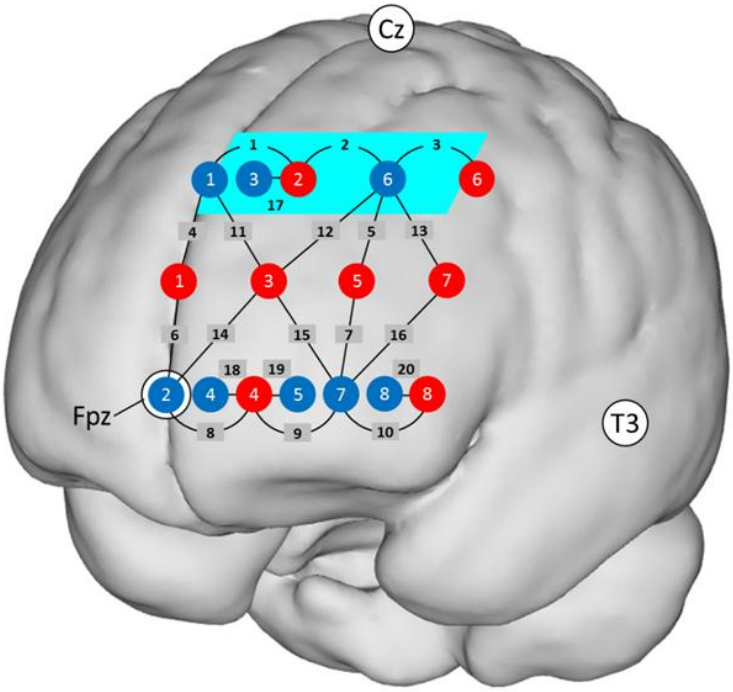

Figure 2. Localization of the 20 channels projected on a standard brain. There were eight detectors (blue dots) and eight emitters (red dots). The black numbers indicate channels. The area highlighted in turquoise (Channels 1, 2, and 3) corresponds to the region of interest (ROI). Channels 1–10 have a source–detector distance of ~30 mm; Channels 11–16, ~42 mm; Channels 17–20, ~15 mm. Detector 2 was placed at Fpz, Source 1 and Detector 1 on an imaginary line towards Cz, and the bottom row of fibers on an imaginary line towards T3.

To remove movement artefacts, a movement artifact removal algorithm (MARA; [55]) was applied. After that, O_2Hb and HHb concentration changes were calculated across the four experimental and the four control blocks, respectively, by means of a general linear model (GLM) model as suggested by Gagnon et al. [56]. All children achieved at least 80% and 50% correct responses in the control and experimental condition, respectively. For statistical analysis, the mean concentration changes in O_2Hb and HHb relative to baseline were calculated within each child for both conditions (control and experimental) and for each channel (Channels 1–16).

2.6. Time Course of the Study

A three-stage procedure was used in the present study. First, over 250 children were screened for mental ability. Then, those children who qualified for either the LA or HA mental ability group performed an adaptive visuospatial WM task to determine the required individual level of task demand

for the subsequent fNIRS measurement. The average interval between the three testing stages was 18 days.

3. Results

All statistical analyses were run with R [57]. The post hoc pairwise comparisons were adjusted for multiple testing with Bonferroni–Holm correction [58].

3.1. Behavioral Data

The mean WM span (± standard deviation) of the total sample was 4.0 ± 0.98. For the LA and the HA groups, mean WM spans were 3.8 ± 1.00 and 4.3 ± 0.94, respectively. When performing the individually adjusted WM task during fNIRS measurement, the mean percentages of correct responses across all participants were 99.5 ± 1.3% and 92.1 ± 6.1% for the active control and the experimental condition, respectively, $t(41) = 7.88$, $p < 0.001$, $d = 1.67$. This finding clearly shows that the task demands were significantly higher in the experimental than in the active control condition. At the same time, percentages of correct responses did not differ significantly between the LA and HA group in the experimental condition; mean percentages of correct responses were 91.4 ± 6.2% and 92.6 ± 6.2% for the LA and the HA group, respectively, $t(40) = 0.62$, $p = 0.54$, $d = 0.19$. Thus, we accomplished our goal of obtaining equivalent levels of subjective task difficulty for both mental ability groups.

3.2. fNIRS Data

Definition of the region of interest (ROI): In order to enable a best possible replication of Witmer et al.'s [27] findings, we investigated the same ROI, located in BA 8, and used the same exploratory approach. This ROI was represented by the Channels 1 to 3. The MNI coordinates (x, y, z) of Channels 1 to 3 were (−8, 48, 48), (−27, 40, 48), and (−42, 25, 48), respectively. In all three channels a negative correlation between O_2Hb and HHb could be observed, caused by an increase in O_2Hb and a decrease in HHb. This typical hemodynamic response pattern during functional activation [6] was a good indication that the signal did not contain systemic changes [6,59] and demonstrated high signal quality [8]. The mean concentration changes in O_2Hb and HHb of Channels 1 to 3 were averaged and, thus, provided the value for our ROI. Within this ROI, the negative correlations between O_2Hb and HHb were significant for both conditions ($r_{control} = -0.46$, $r_{experimental} = -0.53$ (both p values <0.01, two-tailed)). Figure 2 shows a projection of the ROI onto a standard brain. Obtained concentration changes in O_2Hb and HHb as a function of fNIRS condition are presented in Table 1, for the total sample as well as for the LA and the HA groups.

Table 1. Mean (*M*) and standard deviation (*SD*) of oxygenated (O_2Hb) and deoxygenated (HHb) hemoglobin concentration changes as a function of functional near-infrared spectroscopy (NIRS) condition (control and experimental) for the total sample (Total, $N = 42$) as well as for the lower (LA, $n = 18$) and higher (HA, $n = 24$) mental ability groups.

Hemoglobin Oxygenation	Condition	Total		LA		HA	
		M	*SD*	*M*	*SD*	*M*	*SD*
O_2Hb	control	0.23	0.54	0.15	0.59	0.29	0.49
	experimental	0.40	0.53	0.54	0.57	0.29	0.48
HHb	control	−0.01	0.22	−0.03	0.25	0.01	0.19
	experimental	−0.05	0.23	−0.08	0.23	−0.03	0.23

Next, we assessed our two main hypotheses derived from Witmer et al.'s [27] study. First, changes in functional activation while performing the WM task were expected to be specific to visuospatial WM-related processes and not related to more general subsidiary processes. Second, the individual level of mental ability was predicted to effectively moderate the concentration changes

in Hb oxygenation during the processing of the visuospatial WM task. More precisely, substantial functional activation was expected for the LA but not for the HA group. To verify our hypotheses, a three-way analysis of variance was performed with Hb oxygenation (O_2Hb and HHb) and task condition (experimental and control) as the two within-subject factors and mental ability (LA and HA) as a between-subjects factor.

This analysis yielded a significant main effect of Hb oxygenation, $F(1, 40) = 13.76$, $p < 0.001$, $\eta_p^2 = 0.256$, indicating a much more pronounced change in O_2Hb than HHb concentration. Neither the main effect of task condition, $F(1, 40) = 2.24$, $p = 0.142$, $\eta_p^2 = 0.053$, nor the main effect of mental ability, $F(1, 40) = 0.02$, $p = 0.892$, $\eta_p^2 < 0.001$, reached the 5% level of statistical significance. There was, however, a statistically significant two-way interaction of Hb oxygenation and task condition, $F(1, 40) = 6.38$, $p = 0.016$, $\eta_p^2 = 0.138$, as well as a statistically significant three-way interaction of all factors combined, $F(1, 40) = 4.24$, $p = 0.046$, $\eta_p^2 = 0.096$. No significant two-way interactions were found for Hb oxygenation and mental ability, $F(1, 40) = 0.27$, $p = 0.601$, $\eta_p^2 = 0.007$, or for task condition and mental ability, $F(1, 40) = 3.63$, $p = 0.064$, $\eta_p^2 = 0.083$.

With regard to the significant two-way interaction of Hb oxygenation and task condition, post hoc pairwise comparisons revealed that the O_2Hb concentration was significantly higher than the HHb concentration in the active control condition, $t(41) = 2.28$, $p = 0.028$, $d = 0.57$. Furthermore, in the experimental condition, an increase in O_2Hb and a concomitant slight decrease in HHb resulted in a highly significant difference between the O_2Hb and the HHb concentrations, $t(41) = 4.26$, $p < 0.001$, $d = 1.09$ (see Figure 3). This pattern of changes in O_2Hb and HHb concentrations is consistent with the notion that the observed functional brain activation can be considered specific to visuospatial WM-related processes rather than reflecting more general subsidiary processes.

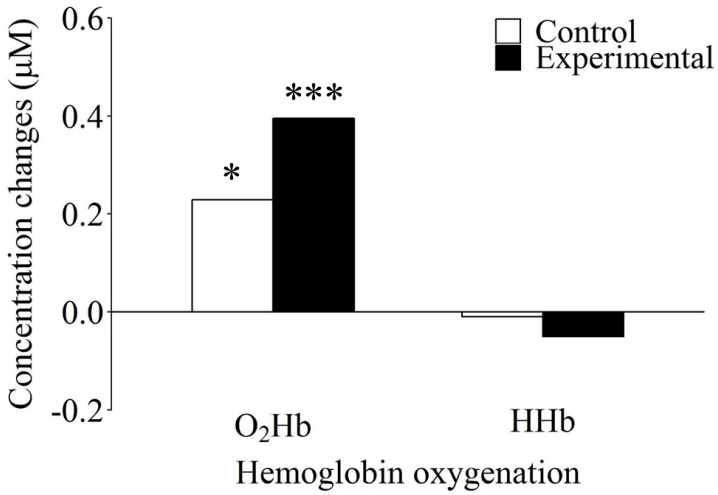

Figure 3. Differences in concentration changes for oxygenated (O_2Hb) and deoxygenated (HHb) hemoglobin as a function of condition for the working memory task. Within the control and the experimental condition, there was a significant difference in concentration change between O_2Hb and HHb. *: significantly different from HHb concentration change in the active control condition ($p < 0.05$). ***: significantly different from HHb concentration change in the experimental condition ($p < 0.001$).

Regarding the statistically significant three-way interaction, it should be noted that the occurrence of functional brain activation might be differentially affected by an individual's level of mental ability. To assess the interaction more thoroughly, two separate two-way analyses of variance were conducted with the within-subject factors Hb oxygenation and task condition for the LA and the HA groups, respectively. For the LA group, a statistically significant main effect of Hb oxygenation, $F(1, 17) = 7.12$, $p = 0.016$, $\eta_p^2 = 0.295$, indicated a higher O_2Hb concentration compared with that of HHb. No significant main effect of task condition, $F(1, 17) = 2.79$, $p = 0.113$, $\eta_p^2 = 0.141$,

was revealed. Most importantly, however, the interaction between these two factors became also significant, $F(1, 17) = 7.40$, $p = 0.015$, $\eta_p^2 = 0.303$. Post hoc pairwise comparisons indicated that the O_2Hb concentration was significantly higher in the experimental than in the active control condition, $t(17) = 2.26$, $p = 0.037$, $d = 0.66$. Unlike O_2Hb, no significant difference in HHb concentration between the experimental and the active control condition could be revealed, $t(17) = 0.74$, $p = 0.235$, $d = 0.19$. For the active control condition, no indication of a significant difference between O_2Hb and HHb concentration was found, $t(17) = 1.07$, $p = 0.198$, $d = 0.39$. In the experimental condition, however, there was a significant difference between O_2Hb and HHb due to the increase in O_2Hb and a slight concomitant decrease in HHb concentration, $t(17) = 3.62$, $p = 0.004$, $d = 1.41$ (see left panel of Figure 4).

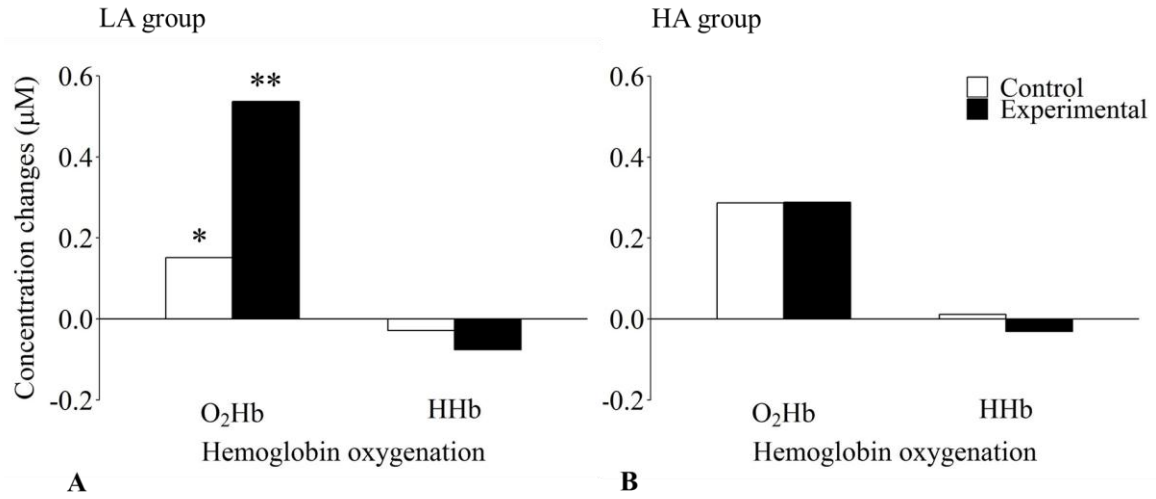

Figure 4. Effects of level of mental ability and condition on hemoglobin oxygenation concentration changes for the working memory task in the lower (LA; Panel **A**) and the higher (HA; Panel **B**) mental ability group. The lower mental ability group showed significantly increased oxygenated hemoglobin (O_2Hb) and significantly decreased deoxygenated hemoglobin (HHb) concentrations in the experimental compared to the active control condition. No significant differences could be observed for the higher mental ability group. *: significantly different from O_2Hb concentration change in the experimental condition ($p < 0.05$). **: significantly different from HHb concentration change in the experimental condition ($p < 0.01$).

As in the LA group, a two-way analysis of variance for the HA group yielded a statistically significant main effect of Hb oxygenation, $F(1, 23) = 6.40$, $p = 0.019$, $\eta_p^2 = 0.218$, but no statistically significant main effect of task condition, $F(1, 23) = 0.24$, $p = 0.627$, $\eta_p^2 = 0.010$. In contrast to the LA group, there was no indication of a statistically significant interaction between Hb oxygenation and task condition, $F(1, 23) = 0.16$, $p = 0.698$, $\eta_p^2 = 0.007$ for the HA group (see right panel of Figure 4). Thus, the additional analysis of the statistically significant three-way interaction confirmed functional brain activation elicited by visuospatial WM-specific processes in the participants with lower mental ability, whereas in the participants with higher mental ability no evidence of functional activation could be identified.

4. Discussion

The major aim of the present study was to replicate two results of the study by Witmer et al. [27]: (1) the sensitivity of fNIRS recordings for measuring visuospatial WM-specific processes and (2) the moderating effect of mental ability on functional activation. An additional goal was to test whether these results can be generalized to a children sample.

Because fNIRS is markedly less burdensome for subjects than other neuroimaging procedures (e.g., fMRI or PET), it is often used for WM studies in children (e.g., [60–62]). For this reason,

the generalizability of Witmer et al.'s [27] results to a children sample is important from a use-inspired perspective. Furthermore, due to children's shorter scalp–brain distance at the forehead [63], fNIRS recordings in children provide a better signal-to-noise ratio and, thus, a clearer signal than recordings in adult subjects [26,35,36,64]. Hence, from a methodological perspective, fNIRS recordings in children, from which possible movement artifacts were carefully removed, should yield an enhanced signal quality compared with the adult sample investigated by Witmer et al. [27].

The pronounced functional activation elicited by visuospatial WM-specific task demands in the experimental compared with the active control condition, as observed in the present study, clearly confirmed Witmer et al.'s [27] finding. These concordant results provide converging evidence that fNIRS recordings are sensitive enough to reflect visuospatial WM-specific processes in both children and young adults.

The replication of the moderating effect of mental ability on functional activation was also successful in the children sample. In the LA group, the visuospatial WM-specific task demands of the experimental condition induced the typical pattern of functional activation, whereas in the active control condition no functional activation took place. In contrast, the HA group showed no indication of functional activation in either condition. This consistency with the outcome of Witmer et al.'s [27] study indicates that the differential effect of mental ability on functional brain activation is a fundamental phenomenon that not only occurs in adults but can also be detected in the developing brain of children.

A similar differential pattern of functional activation as a function of mental ability in adult subjects has been reported in previous PET studies [38,39], SPECT studies [37], fMRI studies [40–44], and an fNIRS study [45]. All these studies revealed that LA individuals show much more pronounced functional activation than HA individuals when processing cognitive tasks with low to moderate levels of task difficulty. It is important to note, however, that HA individuals consistently performed better than LA individuals when processing the same WM task. This latter finding clearly indicates that a given cognitive task with low to moderate difficulty is subjectively less demanding for HA compared to LA individuals. Therefore, it cannot be ruled out that this inequality in subjective task demand may have caused the observed differences in brain activation between LA and HA individuals.

To control for this crucial issue, we applied the same adaptive approach as Witmer et al. [27]. By adopting this approach, we ensured that each child was presented with a task that was individually adjusted for difficulty, to obtain a virtually identical level of subjective task demand irrespective of the child's individual level of mental ability. At the behavioral level, this was confirmed by the fact that the percentages of correct responses in the experimental condition did not differ significantly between the LA and HA group. Despite the virtually identical subjective task demand for all children, the difference in functional brain activation between the LA and HA children was still present. This provides clear evidence against the notion that the observed differences in functional brain activation originate from differences in subjective task demand. Rather, LA children seemed to require more cortical oxygen compared with HA children for solving the visuospatial WM task adjusted for subjective task demand.

A comparison of the children's data in the present study with the data of the young adults from the study by Witmer et al. [27] revealed that measured hemodynamic responses and, in particular, changes in O_2Hb were markedly larger in the children sample by a factor of nearly four for both the experimental and the active control condition. Mean changes in O_2Hb were 0.05 and 0.23 in the adult and children sample, respectively, in the control condition. Similarly, in the experimental condition, mean O_2Hb changes were 0.14 and 0.40 for the adult and children sample, respectively. Such a difference in activation strength of the frontal lobe between children and young adults has also been reported in previous fMRI (e.g., [65–67]) and fNIRS [62] studies. The common aspect of these studies was that although they found activation in the same frontal brain areas for children and adults during processing of the same task, the activation was markedly stronger in children than in adults.

For fNIRS studies, the shorter scalp–brain distance in children provides the most reasonable explanation for this observation [35]. Cui et al. [26] and Strangman et al. [36] demonstrated that scalp–brain distances affect the photon path and have a direct impact on fNIRS data quality as

indicated by the signal-to-noise ratio. As the scalp–brain distance at the forehead is substantially shorter in children than in adults, the signal-to-noise ratio of fNIRS recordings in children seems to be much better than that of adult subjects.

This aspect is also relevant for the interpretation of the differential effect of mental ability on functional activation in the present study. In the LA group, the expected functional brain activation pattern became even clearer (compared with adults), whereas in the HA group, there were no signs of functional activation despite the improved signal quality. Thus, the absence of functional brain activation in the HA group cannot be accounted for by a methodological artifact due to blurred signal, but represents a genuine null result [68].

One major methodological challenge of fNIRS technology is the fact that the NIRS signal reflects not only the genuine cortical hemodynamic response evoked by the experimental task, but also extracerebral hemodynamic effects [6,69,70]. These latter effects can mimic or mask the genuine cortical hemodynamic response [6]. To cope with this problem, a multidistance approach (e.g., [25,71–73]) was applied in the present study. This procedure enabled us to use the short channels to regress out superficial influences from the longer channels [52].

Another methodological issue of the present study is age- or maturation-related differences in the head size of children [74]. Substantial deviations may have resulted in channel locations that did not correspond to our specified ROI. For this reason, we used a 3D digitizer to measure the locations of the optodes and calculate the locations of the channels as described in Singh, Okamoto, Dan, Jurcak, and Dan [75]. This approach allowed for the identification of children whose channel locations did not correspond to our specified ROI.

5. Conclusions

Taken together, we successfully replicated two major findings reported by Witmer et al. [27]. By confirming that fNIRS is sensitive enough to assess hemodynamic responses directly related to cognitive processes elicited by a visuospatial WM task, we provide additional converging evidence for the validity and sensitivity of fNIRS recordings. Furthermore, we were able to replicate the mental-ability-induced differences in functional activation. Moreover, by testing a children sample, we were also able to generalize the validity of Witmer et al.'s [27] findings in young adults to 11- to 13-year-old children. This latter aspect seems to be of particular significance considering the relatively large number of fNIRS studies on WM performance in children.

Author Contributions: T.H.R. and S.J.T. conceived of and designed the experiments. J.S.W. and E.A.A. set up the experiment. J.S.W. and E.A.A. performed the experiment. A.J.M. wrote the analysis script and supported the data preparation. J.S.W. analyzed the data. T.H.R. and J.S.W. wrote the paper.

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Conflicts of Interest: The authors declare no conflict of interest.

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