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A Within-Sample Comparison of Two Innovative Neuropsychological Tests for Assessing ADHD

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Summary: A Within-Sample Comparison of Two Innovative Neuropsychological Tests for Assessing ADHD

Adult ADHD is a complex disorder that is assessed by various diagnostic instruments. Currently, clinical exploration, interviews and questionnaire data play the most important role in the diagnostic process. Although patients show multiple cognitive impairments, the use of neuropsychological continuous performance tests (CPTs) is only mentioned supplementary in clinical guidelines. Validity and usefulness of CPTs in ADHD patients is generally discussed critically due to the lack of sensitivity and specificity [1]. Multidimensional approaches, combining different neuropsychological assessments with clinical measures, are expected to improve the establishment of an ADHD diagnosis in adulthood [2]. The current study aims to investigate two different CPTs in a head-to-head comparison regarding their comparability and link with clinical parameters. To our knowledge, a head-to-head comparison of these innovative tests within one same sample has not yet been made but might have important implications for test selection and clinical routing. The clinical sample was recruited from unselected adult patients presenting to the ADHD outpatient clinic of the Department of Psychiatry, Psychosomatic Medicine, and Psychotherapy, University Hospital Frankfurt, for diagnostic assessment of possible ADHD between May and November 2019. The patients were seen by experienced clinicians to assess current and former symptoms in adulthood and childhood with the use of the structured diagnostic interview for ADHD in adults (DIVA 2.0) [3]. Childhood school records, medical history including former substance abuse, mental disorders, comorbidities, somatic disorders, and family anamnesis of ADHD were assessed. Patients were interviewed with the Wender-Reimherr Interview (WRI) [4] by an independent trained interviewer and were asked to fill out the following self-report instruments: short form of the Wender-Utah Rating Scale (WURS-k) [5], Impulsive Behavior Scale (UPPS) [6] and the General Health Questionnaire (GHQ-28) [7]. All patients were tested with two continuous performance tests: the Quantified Behavior Test (Qb-Test) [8] and Nesplora Aquarium [9]. The Qb-Test measures not only inattention and impulsivity but also hyperactivity with

the use of an infrared camera and a reflector attached to a headband to record movements during the test. In Nesplora Aquarium, a virtual reality CPT, motor activity is measured through VR optical devices equipped with sensors and headphones. The overall comparability of the tests was limited. Despite the congruent measure of inattention in both tests, no correlation with clinical parameters was found. Hyperactivity was positively associated with current ADHD symptoms in both tests. Hyperactivity in the Qb-Test additionally reflected childhood ADHD symptoms. Although the hyperactivity factors of both tests are independent, they nevertheless seem to be related to one of the most valid clinical symptom components. Impulsivity was represented independently by both tests and poorly associated with clinical features. Qb-Test's factor impulsivity did not correlate with measures of impulsivity in Nesplora Aquarium at all, questioning whether there is a homogenous impulsivity construct across neuropsychological tests and clinical symptoms. Taken together, the current study enables a good comparison of the two CPTs and reveals detailed information on their compatibility with clinical measures. Inattention is a basic factor, which overlaps between the two tests in each subject. As it fails to predict clinical parameters, this highlights the problem in linking subjective and objective methods in diagnosing ADHD [10]. The current findings question the simple use of so-called objective measures in clinical ADHD diagnosis because of questionable validity. The findings emphasize the need for a new approach in diagnosis in the sense of precision medicine, going beyond conventional classification systems to enable suitable individual solutions for diagnosis and treatment [11].

Due to these findings, this dissertation discusses the gold standard of current ADHD diagnosis in the light of the existing guidelines and possible starting points for improvement. The investigated continuous performance tests are thus reviewed in consideration of the quality criteria of good diagnostic procedures. The potential of neuropsychological tests with regard to increasing objectivity, validity and differentiation of diagnoses is examined. Finally a recommendation regarding the use of neuropsychological tests in clinical practice is made.

Zusammenfassung: Vergleich zweier innovativer neuropsychologischer Testverfahren zur Bewertung von ADHS

ADHS im Erwachsenenalter ist eine komplexe Erkrankung, die durch verschiedene diagnostische Instrumente erfasst wird. Aktuell spielen dabei vor allem die klinische Exploration, Interview- und Fragebogendaten eine Rolle. Obwohl bei Patient*innen vielfältige kognitive Einschränkungen bestehen, wird die Verwendung neuropsychologischer Daueraufmerksamkeitstests (CPTs) in den klinischen Leitlinien nur ergänzend erwähnt. Validität und Nützlichkeit von CPTs bei ADHS Patient*innen wird aufgrund der mangelnden Sensitivität und Spezifität immer wieder kritisch diskutiert [1]. Multidimensionale Ansätze, in denen verschiedene neuropsychologische Beurteilungen mit klinischen Parametern kombiniert werden, sollen das Aufstellen einer ADHS Diagnose im Erwachsenenalter verbessern [2]. Die vorliegende Studie untersucht zwei verschiedene CPTs bezüglich deren Vergleichbarkeit und deren Verknüpfung mit klinischen Parametern. Ein direkter Vergleich innerhalb derselben Stichprobe ist bisher nicht durchgeführt worden, könnte jedoch wichtige Implikationen für die Testauswahl und darauffolgende klinische Interventionen haben. Die klinische Stichprobe besteht aus zufällig ausgewählten erwachsenen Patient*innen, die sich in der ADHS Ambulanz der Klinik für Psychiatrie, Psychosomatik und Psychotherapie des Universitätsklinikums Frankfurt zur diagnostischen ADHS Beurteilung zwischen Mai und November 2019 vorstellten. Die Patient*innen wurden von erfahrenen Ärzt*innen mithilfe des strukturierten diagnostischen Interviews für ADHS bei Erwachsenen (DIVA 2.0) [3] befragt. Außerdem wurden Schulzeugnisse bewertet und die medizinische Vorgeschichte erhoben. Anschließend wurden die Patient*innen mit dem Wender-Reimherr Interview (WRI) [4] von einer unabhängigen Interviewerin befragt und füllten die folgenden Selbstbeurteilungsfragebögen aus: Kurzform der Wender-Utah Rating Scale (WURS-k) [5], Impulsive Behavior Scale (UPPS) [6] und General Health Questionnaire (GHQ-28) [7]. Alle Patient*innen nahmen anschließend an der Testung mit zwei CPTs teil: dem Quantified Behavior Test (Qb-Test) [8] und Nesplora Aquarium [9]. Der Qb-Test misst neben Unaufmerksamkeit und Impulsivität auch Hyperaktivität mithilfe

einer Infrarot Kamera und eines Reflektors, welche das Bewegungsmuster während der Testung aufzeichnen. In Nesplora Aquarium wird virtuelle Realität genutzt, um das Bewegungsmuster mithilfe eines optischen Gerätes, das mit Sensoren und Lautsprechern ausgestattet ist, aufzuzeichnen. Es zeigte sich, dass die übergreifende Vergleichbarkeit beider Tests begrenzt ist. Trotz der kongruenten Messung von Unaufmerksamkeit in beiden Tests konnten keine Korrelationen mit den klinischen Parametern festgestellt werden. Hyperaktivität ist in beiden Tests positiv mit aktuellen ADHS Symptomen assoziiert, wobei der Qb-Test darüber hinaus noch Korrelationen mit ADHS Symptomen aus der Kindheit aufweist. Impulsivität stellte sich als ein unabhängiges Konstrukt heraus, sowohl die Korrelation zwischen beiden Tests als auch die Assoziation mit klinischen Parametern betreffend. Dies stellt in Frage, ob ein homogenes Impulsivitätskonstrukt existiert, welches sich in neuropsychologischen Tests und klinischen Symptomen abbildet. Insgesamt ermöglicht die Studie einen guten Vergleich beider CPTs und zeigt detaillierte Informationen über die Kompatibilität mit klinischen Symptomen auf. Unaufmerksamkeit stellte sich als ein basaler Faktor heraus, der zwischen beiden Tests über alle Patient*innen hinweg überlappt. Da dieser Faktor jedoch nicht mit klinischen Parametern korreliert, unterstreicht dies die Problematik, subjektive mit objektiven Methoden in der ADHS Diagnostik zu verbinden [10]. Die aktuellen Ergebnisse bezweifeln die einfache Anwendung sogenannter objektiver Messverfahren in der klinischen ADHS Diagnostik aufgrund ihrer fragwürdigen Validität. Die Ergebnisse der Studie verdeutlichen die Notwendigkeit eines neuen diagnostischen Ansatzes im Sinne der Präzisionsmedizin, welcher über die konventionellen Klassifikationssysteme hinaus passende individuelle Lösungen für Diagnostik und Behandlung ermöglicht [11].

In der vorliegenden Dissertation wird auf diesen Ergebnissen basierend der Goldstandard der aktuellen ADHS-Diagnostik unter Beachtung der Leitlinien diskutiert. Die untersuchten CPTs werden unter Berücksichtigung der Gütekriterien guter diagnostischer Verfahren überprüft. Das Potenzial neuropsychologischer Testverfahren im Hinblick auf die Steigerung von Objektivität, Validität und Differenziertheit der Diagnosen wird untersucht und Empfehlungen für die klinische Anwendung formuliert.

Übergreifende Zusammenfassung:

Einleitung:

Die Aufmerksamkeitsdefizit-Hyperaktivitätsstörung (ADHS) ist eine der häufigsten neurologischen Entwicklungsstörungen im Kindesalter [12] und bleibt in 40-55 % der Fälle bis ins Erwachsenenalter bestehen [13]. Menschen mit ADHS sind in verschiedensten Lebensbereichen wie Bildung oder dem Arbeitsumfeld beeinträchtigt [14,15]. Aus diesem Grund benötigen Patient*innen mit ADHS eine präzise Diagnose, die eine spezifische Behandlung ermöglicht. Der aktuellen S3 Leitlinie zufolge ist ADHS eine klinische Diagnose. Die Kardinalsymptome Hyperaktivität, Impulsivität und/oder Unaufmerksamkeit müssen die Kriterien von ICD-10 bzw. DSM-5 erfüllen. Die Symptome müssen in mehreren Lebensbereichen, wie beispielsweise dem schulischen, beruflichen oder familiären Kontext auftreten. Das Auftreten von Symptomen in einzelnen, umgrenzten Lebensbereichen kann eher als ein Hinweis auf das Vorhandensein anderer psychischer Störungen gewertet werden. Als Kriterium für die Diagnosevergabe gilt eine mindestens moderate Beeinträchtigung der Beziehungen, der Leistungsfähigkeit, der Aktivitäten oder der Teilhabe [16]. Aktuell wird der routinemäßige Einsatz verschiedener diagnostischer Instrumente zur Diagnosefindung empfohlen. Die umfassende strukturierte Exploration der Patient*innen stellt dabei einen Kernpunkt des diagnostischen Prozesses dar. Des Weiteren erfolgt eine Verhaltensbeobachtung der Patient*innen in der Untersuchungssituation. Standardmäßig erfolgen außerdem die Erstellung des psychopathologischen Befunds sowie eine körperliche und insbesondere neurologische Untersuchung mit Beurteilung des Entwicklungsstandes. Die Selbsteinschätzung des*der Patient*in wird mithilfe eines diagnostischen Interviews erfasst. Fragebogenverfahren sollten zur vertiefenden Exploration der Symptomatik sowie gegebenenfalls vorhandener Begleitsymptome eingesetzt werden. Psychologische Testverfahren, darunter auch kontinuierliche Leistungstests, werden nicht als Entscheidungskriterium für die Annahme oder Ablehnung der ADHS Diagnose empfohlen sondern sollen lediglich als Ergänzung und zur Beantwortung spezifischer Fragestellungen hinzugezogen werden [16].

Kontinuierliche Leistungstests (CPT) gehören zu den neuropsychologischen Testverfahren, mit denen die Kernsymptome von ADHS wie Unaufmerksamkeit, Hyperaktivität und Impulsivität gemessen werden können. Die Genauigkeit und Nützlichkeit von CPTs bei ADHS-Patient*innen wird jedoch aufgrund ihrer mangelnden Sensitivität und Spezifität kritisch diskutiert [1]. Jüngste Ergebnisse deuten darauf hin, dass ein multidimensionaler Ansatz, bei dem neuropsychologische Beurteilungen in Kombination mit anderen klinischen Instrumenten zum Einsatz kommen, die Aufstellung einer ADHS-Diagnose bei Erwachsenen verbessert [2]. Eine Erweiterung der konventionellen symptombasierten Klassifizierung durch die Integration verschiedener Methoden und Perspektiven kann eine präzisere Diagnose ermöglichen, die für die Einleitung einer angemessenen Behandlung erforderlich ist [11].

Kontinuierliche Leistungstests wurden bereits in vielen Studien, insbesondere bei Kindern und Jugendlichen untersucht. Gegenstand der Untersuchungen war jedoch häufig die Unterscheidung zwischen ADHS-Patient*innen und sich normal entwickelnden Kindern [17, 18]. Was die aktuelle Studie auszeichnet, ist die Untersuchung innerhalb von erwachsenen ADHS-Patient*innen, die es ermöglicht, genauer zu untersuchen, wie klinische Parameter, die aus verschiedenen diagnostischen Instrumenten wie Fragebögen, Interviews und CPTs abgeleitet werden, miteinander verknüpft sind und auf welche Weise sie die tatsächlichen klinischen Symptome widerspiegeln können. In der vorliegenden Dissertation werden aus den Ergebnissen der Studie wichtige Erkenntnisse für die Weiterentwicklung geeigneter Testverfahren abgeleitet, mit dem Ziel, die diagnostischen Methoden und Behandlungsmöglichkeiten sinnvoll zu erweitern. Insbesondere die Möglichkeit der Identifikation von ADHS-Subtypen in „unaufmerksam", „hyperaktiv/impulsiv" oder „kombiniert", wie es beispielsweise das strukturierte diagnostische Interview für ADHS bei Erwachsenen (DIVA 2.0) [3] ermöglicht, wird in Bezug auf die neuropsychologische Testdiagnostik hin untersucht.

Fragestellung:

Korrelieren die Variablen beider CPTs (d. h. Nesplora Aquarium und Qb-Test) im Hinblick auf die ADHS Kardinalsymptome miteinander? Wie ist die ökologische Validität der beiden CPTs (d. h. Nesplora Aquarium und Qb-Test)

zu bewerten? Korrelieren neuropsychologische Daten mit klinischen Ratingskalen und einer persönlichkeitsbasierten Skala für Impulsivität? Welche Implikationen für die klinische Anwendung der CPTs ergeben sich aus der Studie?

Methoden:

Die klinische Stichprobe wurde aus unselektierten erwachsenen Patient*innen rekrutiert, die sich zwischen Mai und November 2019 in der ADHS-Ambulanz der Klinik für Psychiatrie, Psychosomatische Medizin und Psychotherapie des Universitätsklinikums Frankfurt zur diagnostischen Einschätzung einer möglichen ADHS Diagnose vorstellten. Die Patient*innen wurden von erfahrenen Ärzt*innen mithilfe des strukturierten diagnostischen Interviews für ADHS bei Erwachsenen (DIVA 2.0) [3] befragt. Außerdem wurden Schulzeugnisse bewertet und die medizinische Vorgeschichte einschließlich Komorbiditäten, früherem Substanzmissbrauch, somatischen Störungen und familiärer Anamnese von ADHS erhoben. Anschließend wurden die Patient*innen mit dem Wender-Reimherr Interview (WRI) [4] von einer unabhängigen Interviewerin befragt und füllten die folgenden Selbstbeurteilungsfragebögen aus: Kurzform der Wender-Utah Rating Scale (WURS-k) [5], Impulsive Behavior Scale (UPPS) [6] und General Health Questionnaire (GHQ-28) [7]. Alle Patient*innen nahmen anschließend an der Testung mit zwei CPTs teil: dem Quantified Behavior Test (Qb-Test) [8] und Nesplora Aquarium [9]. Die Reihenfolge der Tests wurde in der gesamten Stichprobe randomisiert. Der Qb-Test misst neben Unaufmerksamkeit und Impulsivität auch Hyperaktivität mithilfe einer Infrarot Kamera und eines Reflektors, welche das Bewegungsmuster während der Testung aufzeichnen. In Nesplora Aquarium wird virtuelle Realität genutzt, um das Bewegungsmuster mithilfe eines optischen Gerätes, das mit Sensoren und Lautsprechern ausgestattet ist, aufzuzeichnen. Qb-Tech liefert sowohl einzelne Variablen als auch die drei Hauptkomponenten Unaufmerksamkeit, Impulsivität und Hyperaktivität, die aus einer Hauptkomponentenanalyse abgeleitet wurden. Um einen Vergleich zwischen den Hauptkomponenten des Qb-Tests und den entsprechenden Parametern von Nesplora Aquarium zu ermöglichen, wurde eine Hauptkomponentenanalyse für die Variablen von Nesplora Aquarium

durchgeführt. Um die Vergleichbarkeit der beiden CPTs zu testen, wurden Korrelationsanalysen durchgeführt. Wir haben die fünf Hauptkomponenten aus Nesplora Aquarium, die aus der Hauptkomponentenanalyse abgeleitet wurden, mit den drei Hauptkomponenten des Qb-Tests korreliert, die zuvor von Qbtech berechnet und bereitgestellt wurden. Um einen detaillierteren Einblick in die jeweiligen Beziehungen zwischen den einzelnen Variablen zu ermöglichen, wurden alle Variablen von Nesplora Aquarium und des Qb-Tests, die die Hauptkomponenten bildeten, miteinander korreliert. In einem letzten Schritt wurden Korrelationsanalysen durchgeführt, um die Kompatibilität der beiden CPTs mit klinischen Symptomen zu bewerten. Zum einen wurden die Hauptkomponenten beider CPTs und zum anderen alle von den CPTs gelieferten Variablen mit klinischen Ratingskalen (WRI, WURS-k, GHQ-28) und der persönlichkeitsbasierten Skala (UPPS) korreliert. Obwohl es sich um eine explorative Studie an einer hochspezifischen, kleinen Stichprobe von ADHS-Patient*innen handelte, haben wir bei Bedarf zusätzlich für multiples Testen korrigiert.

Ergebnisse:

Es wurden partielle Korrelationen (unter Kontrolle von Geschlecht, Alter und Reihenfolge der Testdurchführung) zwischen den Hauptkomponenten von Nesplora Aquarium und dem Qb-Test durchgeführt. Es wurde eine signifikante positive Korrelation zwischen den Unaufmerksamkeitsfaktoren von Nesplora Aquarium und dem Qb-Test gefunden (r = 0,49, p = 0,01). Um die Beziehung zwischen den beiden kontinuierlichen Leistungstests weiter zu spezifizieren, wurden partielle Korrelationen (unter Kontrolle von Geschlecht, Alter und Reihenfolge der Testdurchführung) zwischen den zugrunde liegenden Variablen der Hauptkomponenten von Nesplora Aquarium und dem Qb-Test durchgeführt. Hochsignifikante Korrelationen wurden vor allem zwischen den Unaufmerksamkeitsvariablen des Qb-Tests gefunden, die mit Variablen von Nesplora Aquarium korrelieren. In einem nächsten Schritt wurden die neuropsychologischen Daten auf ihre Kompatibilität mit klinischen Symptomen hin untersucht. Unter allen klinischen Parametern zeigte sich, dass der WRI am stärksten mit neuropsychologischen Daten korreliert, wobei zwei Korrelationen hochsignifikant waren: Affektive Labilität im WRI korrelierte negativ mit

Impulsivität im Nesplora Aquarium (r = -0,62, p = 0,008), und Überaktivität im WRI zeigte eine positive Korrelation mit Hyperaktivität im Qb-Test (r = 0,71, p = 0,001). Eine positive signifikante Korrelation wurde zwischen dem WURS-k und Hyperaktivität im Qb-Test festgestellt (r = 0,50, p = 0,04). Die Dringlichkeitssubskala des UPPS korrelierte negativ mit Impulsivität im Qb-Test (r = -0,49, p = 0,046). Es wurden keine signifikanten Korrelationen zwischen dem GHQ-28 und neuropsychologischen Messungen gefunden.

Die beschriebene positive Korrelation zwischen Überaktivität im WRI und Hyperaktivität im Qb-Test erwies sich nach Korrektur für multiples Testen als hoch signifikant (p < 0,006). Zur näheren Untersuchung der Beziehungen zwischen neuropsychologischen Daten und klinischen Symptomen wurden partielle Korrelationen (unter Kontrolle von Geschlecht, Alter und Reihenfolge der Testdurchführung) zwischen den zugrunde liegenden Variablen der Hauptkomponenten von Nesplora Aquarium und des Qb-Tests mit dem WRI, WURS-k, UPPS und GHQ-28 durchgeführt. In Übereinstimmung mit den vorherigen Ergebnissen zeigte der WRI die signifikantesten Korrelationen mit den kontinuierlichen Leistungstests: Überaktivität im WRI korrelierte negativ mit der Diskrepanz der richtigen Antworten (r = -0,63, p = 0,007) im Nesplora-Aquarium, während sie positiv mit der Variable Fläche korrelierte, die die Bewegung im Qb-Test misst (r = 0,63, p = 0,007). Unaufmerksamkeit im WRI korrelierte positiv mit der Einfachheit der Bewegung im Qb-Test (0,64, p = 0,005). Die Korrelation erwies sich nach der Korrektur bei multiplem Testen als hoch signifikant (p < 0,005). Der WRI-Gesamtwert war positiv mit der Bewegung im Nesplora-Aquarium korreliert (r = 0,61, p = 0,009).

Diskussion:

In der vorliegenden Studie wurde Nesplora Aquarium und der Qb-Test in einem stichprobeninternen Vergleich von erwachsenen Patient*innen, die sich in unserer ADHS-Ambulanz vorstellten, miteinander verglichen und die Testparameter mit klinischen Symptomen in Beziehung gesetzt. Die ökologische Validität der beiden CPTs (d.h. Nesplora Aquarium und Qb-Test) wurde im Hinblick auf die Korrelation mit klinischen Ratingskalen (WRI, WURS-k, GHQ-28) und einer persönlichkeitsbasierten Skala (UPPS) bewertet. Die Vergleichbarkeit der Tests war insgesamt begrenzt. Trotz der kongruenten

Messung von Unaufmerksamkeit in beiden Tests wurden keine Korrelationen mit klinischen Symptomen festgestellt. Während Hyperaktivität in beiden Tests positiv mit aktuellen ADHS-Symptomen assoziiert war, spiegelte sie im Qb-Test zusätzlich ADHS-Symptome in der Kindheit wider. Impulsivität wurde in beiden Tests unabhängig voneinander erfasst und war nur schwach mit klinischen Symptomen und dem UPPS assoziiert. Neben der Bewertung der diagnostischen Genauigkeit von CPTs, wie sie bereits in einer Reihe von Studien durchgeführt wurde [17,1], ermöglicht unsere Studie einen differenzierteren Blick auf die verschiedenen Merkmale von ADHS sowie darauf, wie gut sie durch neuropsychologische Tests abgebildet werden. Unaufmerksamkeit, die hauptsächlich von der Testleistung abhängt, ist ein grundlegender Faktor, der sich bei jedem*jeder Proband*in in beiden Tests überschneidet. Da Unaufmerksamkeit klinische Parameter nicht vorhersagen kann, verdeutlicht dies das bereits beschriebene Problem der Verknüpfung subjektiver und objektiver Methoden bei der Diagnosestellung von ADHS [10]. Ein interessanter Testparameter ist die Hyperaktivität, die in beiden Tests aktuelle ADHS-Symptome widerspiegelt, während sie im Qb-Test zusätzlich mit ADHS-Symptomen in der Kindheit assoziiert ist. Da es derzeit nur wenige Erkenntnisse über die Kompatibilität von Nesplora Aquarium mit klinischen Parametern aktueller und kindlicher ADHS-Symptome gibt, sollte diese Frage in weiteren Studien untersucht werden. Die aktuellen Ergebnisse stellen die Verwendung sogenannter objektiver Maße in der klinischen ADHS-Diagnostik aufgrund ihrer fragwürdigen Validität in Frage.

Validität und Reliabilität sind Gütekriterien, die im Rahmen der klassischen Testtheorie [19] beschrieben werden. Jedes Messverfahren unterliegt Messfehlern, welche durch die Anwendung valider und reliabler Testverfahren auf ein Minimum reduziert werden können. Die Tatsache, ob ein psychologisches Messinstrument auch wirklich das Merkmal bzw. Konstrukt erfasst, das es erfassen soll, wird dabei durch die Konstruktvalidität beschrieben. Die Konstruktvalidität stellt ein Maß der internen Validität dar. Besonders interessant für die vorliegende Studie sind zudem die Maße der externen Validität, welche sich dadurch auszeichnen, dass Merkmale, die unter kontrollierten Bedingungen gemessen werden, sich auch auf andere Orte,

Situationen und Zeitpunkte übertragen lassen. Insbesondere die ökologische Validität ist ein Aspekt, der durch die Verwendung von virtueller Realität in kontinuierlichen Leistungstests verbessert werden soll, indem die Nähe zu alltäglichen Situationen hergestellt wird [20]. In diesem Zusammenhang ist ebenfalls die Reliabilität als ein Kernpunkt guter diagnostischer Instrumente zu nennen. Ein Test ist besonders reliabel, wenn er zuverlässig über die Zeit gleiche Ergebnisse unter gleichen Voraussetzungen erzeugen kann. Beispielsweise lässt sich durch die Test-Retest-Reliabilität überprüfen, wie sich ADHS Symptome über die Zeit verändern. Dabei ist die Reliabilität stark von der Homogenität bzw. Heterogenität der Stichprobe abhängig. Je geringer die Varianz der Werte in homogenen Stichproben ausfällt, desto geringer wird die geschätzte Reliabilität im Vergleich zu heterogeneren Stichproben mit größerer Varianz sein [20].

Im Rahmen der umfassenden ADHS Diagnostik fließen Informationen aus verschiedenen Quellen von Ärzt*innen, Lehrer*innen, Patient*innen sowie aus Schulzeugnissen und Berichten zusammen, wobei Unstimmigkeiten zwischen den Beurteilungen die Reliabilität beeinflussen kann. Erschwerend kommt hinzu, dass das berufliche Umfeld als einer der Hauptlebensbereiche, in denen ADHS Symptome auftreten, von Patient*in zu Patient*in stark unterschiedlich sind, was Vergleiche zwischen Patient*innen erschwert. Im Kindes- und Jugendalter ist das schulische Umfeld daher besser geeignet, um Kriterien in größeren Stichproben zu vergleichen. Retrospektive Erinnerungen von Patient*innen können verzerrt und damit unzuverlässig sein. Außerdem haben Patient*innen möglicherweise Kompensationsmechanismen entwickelt, welche ADHS-Symptome verschleiern [21]. Eine möglicherweise gering ausgeprägte Objektivität und Interrater-Reliabilität soll durch den Einsatz objektiver neuropsychologischer Testverfahren verbessert werden, damit die Diagnose robuster wird [1]. Es zeigte sich in einer Untersuchung, dass ADHS Diagnosen bei Kindern, welche durch den Qb-Test ergänzt wurden, über den Zeitraum von einem Jahr im Sinne der Retest Reliabiltiät robuster waren. In der Gruppe, bei der die Beurteilung nur klinisch erfolgte, wurde die ADHS Diagnose zunächst weniger häufig gestellt und ein Jahr später dann doch vergeben [22].

Bei Sensitivität und Spezifität handelt es sich um statistische Größen, die unabhängig von der Prävalenz einer Erkrankung die Güte eines diagnostischen Tests bewerten. Ein Test, der erkrankte Patient*innen auch tatsächlich als krank klassifiziert, besitzt eine hohe Sensitivität. Tests, bei denen Nichterkrankte als gesund erkannt werden, gelten als besonders spezifisch. Berechnet man den Anteil an richtig positiven aus allen Testergebnissen, erhält man den positiv prädiktiven Wert (PPW). Dieser ist definiert als die Wahrscheinlichkeit, dass eine positiv getestet Person auch tatsächlich erkrankt ist. Der Anteil der richtig negativ getesteten an allen negativen Testergebnissen ist definiert als der negativ prädiktive Wert (NPW). Er gibt Auskunft über die Wahrscheinlichkeit, dass ein*e Patient*in mit negativem Testergebnis auch tatsächlich gesund ist [20]. Im Gegensatz zu Sensitivität und Spezifität sind der PPW und NPW abhängig von der Prävalenz der Erkrankung. Mit höherer Prävalenz steigt auch der positiv prädiktive Wert. Das bedeutet im Umkehrschluss, dass positive Werte bei sehr niedriger Prävalenz auch leicht falsch-positiv sein können [23]. Es wird daher empfohlen, diagnostische Tests nur bei klarer Indikation einzusetzen, bei einem Patient*innenkollektiv mit eindeutigen Hinweisen auf das Vorliegen der Erkrankung und nicht bei jedem*jeder Patient*in, da die Aussagekraft des positiven Testwertes bei niedriger Prävalenz vermindert und somit der klinische Nutzen nicht gegeben ist [24].

Bisherige Forschungsergebnisse zeigen, dass die Gütekriterien des Qb-Tests hinsichtlich Sensitivität und Spezifität unzureichend sind. In der Abgrenzung von ADHS zu anderen psychischen Störungen bei Erwachsenen liegen Sensitivität und Spezifität bei den Parametern Unaufmerksamkeit und Impulsivität auf Zufallsniveau. Allein Hyperaktivität hat eine Sensitivität von 76% und eine Spezifität von 40% [10]. Dies legt nahe, dass die Qb-Testergebnisse nur von erfahrenen Kliniker*innen in der Gesamtschau mit den klinischen Symptomen zu bewerten sind. Die positiv prädiktiven Werte der drei Kardinalparameter Unaufmerksamkeit, Impulsivität und Hyperaktivität lagen in bisherigen Studien zwischen 76% und 86%. Dies bedeutet, dass positiv getestete Personen zu 76%-86% auch ADHS haben. Mit negativ prädiktiven Werten von 37%-50% sind negativ getestete Personen nur in 37%-50% der

Fälle auch wirklich gesund [1]. Eine weitere Studie untersuchte die diskriminative Validität neuropsychologischer Testverfahren, unter anderem den Qb-Test, im Vergleich zu dem strukturierten diagnostischen Interview für ADHS bei Erwachsenen (DIVA 2.0) [3]. Das DIVA Interview erwies sich als genauestes Instrument (Accuracy 82,4%, Sensitivität 90%, Spezifität 73%) [25]. Alle untersuchten neuropsychologischen Tests jedoch zeigten Sensitivitäts- und Spezifitätswerte auf Zufallsniveau. Allein der Kardinalparameter Hyperaktivität im Qb-Test erwies eine recht hohe Sensitivität von 76% und eine niedrige Spezifität von 44%, analog zu früheren Forschungsergebnissen [10]. Der Goldstandard der letztendlichen Diagnosevergabe durch erfahrene Kliniker*innen ist aktuell also unverändert gültig. Die vorliegende Studie konnte in Bezug auf Hyperaktivität zeigen, dass diese, gemessen im Qb-Test und in Nesplora Aquarium, mit aktuellen ADHS Symptomen, gemessen auf mehreren Skalen des Wender-Reimherr-Interviews, korreliert. Hyperaktivität im Qb-Test reflektiert außerdem ADHS Symptome aus der Kindheit, wie die Korrelationen mit dem WURS-k nahelegen.

Die Ergebnisse der vorliegenden Studie verdeutlichen in Übereinstimmung mit früheren Untersuchungen, dass die erwünschte Verbesserung der Präzision der ADHS Diagnostik durch den Einsatz neuropsychologischer Testverfahren nicht erreicht werden kann. Es fehlt der Mehrwert, wie es beispielsweise die Mammographie mit einer Sensitivität von ca. 80% in der Früherkennung des Mammakarzinoms leistet [26]. Bei Teilnehmerinnen am Mammographie-Screening ist die Mortalität gegenüber Nicht-Teilnehmerinnen um ca. 20% reduziert [27]. Tests, die zur Überdiagnostizierung von Krankheiten führen, wie es beim PSA-Screening in der Detektion des Prostatakarzinoms der Fall ist, da dieses eine hohe Sensitivität (ca. 90%) bei geringer Spezifität (ca. 20%) aufweist, sind insgesamt kritisch zu bewerten [28]. Zur sinnvollen Verwendung neuropsychologischer Tests als Screeningmethode sind hohe Sensitivitätswerte erforderlich, welche bei dem Qb-Test und Nespolora Aquarium nicht gegeben sind. Zum sicheren Ausschluss einer möglichen ADHS Diagnose werden gleichzeitig hohe Spezifitätswerte benötigt, welche bei diesen Tests ebenfalls nicht vorhanden sind. Auch eine Untergliederung in ADHS-Subtypen kann durch die untersuchten Verfahren nicht geleistet werden [10;1]. Die

untersuchten Tests können ähnlich wie der Einschluss des Hormons BNP (brain natriuretic peptide) in der Herzinsuffizienz Diagnostik, welches sich als ein überflüssiger Parameter in der Diagnostik erwies und die Diagnosefindung nicht verbesserte, gewertet werden [29].

Virtual reality Tests, die vor allem der Verbesserung der ökologischen Validität dienen sollen, wurden bislang vor allem im Hinblick auf die Anwendbarkeit und Umsetzbarkeit im klinischen Setting untersucht. Studien, die umfassend psychometrische Maße an großen Stichproben untersuchen, fehlen weitgehend. Gleiches gilt für die Standardisierung der Tools [30]. Die Ergebnisse der vorliegenden Studie unterstreichen die Notwendigkeit eines neuen Ansatzes in der Diagnostik im Sinne der Präzisionsmedizin, der über herkömmliche Klassifikationssysteme hinausgeht und geeignete individuelle Lösungen für Diagnose und Behandlung ermöglicht [11]. Im Hinblick auf die gewünschte Leistung kognitiver Tests, einen breiten klinischen Phänotyp in verschiedene behandlungsrelevante Untergruppen zu unterteilen [31], zeigen unsere Ergebnisse, dass solche kognitiven Tests schwer zu etablieren sind. Obwohl kontinuierliche Leistungstests die Diagnose verbessern sollen, ist die Validität des aktuellen Tests nicht ausreichend belegt, da beispielsweise die Impulsivitätsmaße in beiden Tests nicht mit klinischen Parametern, die mit der ADHS-Impulsivität zusammenhängen, korrelieren. Wie zu erwarten sind beide Tests durch die Komponente Unaufmerksamkeit miteinander verbunden. Da diese Messung der grundlegenden Testleistung jedoch keine klinische Repräsentation zu haben scheint, würden wir derzeit keinen der beiden Tests als einen Schritt im diagnostischen Arbeitsablauf verwenden. Die bewegungsbezogenen Parameter sind jedoch vielversprechend und sollten in zukünftigen Forschungen in stark phänotypisierten Stichproben validiert werden.

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Article

A Within-Sample Comparison of Two Innovative Neuropsychological Tests for Assessing ADHD

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Abstract: New innovative neuropsychological tests in attention deficit hyperactivity disorder ADHD have been proposed as objective measures for diagnosis and therapy. The current study aims to investigate two different commercial continuous performance tests (CPT) in a head-to-head comparison regarding their comparability and their link with clinical parameters. The CPTs were evaluated in a clinical sample of 29 adult patients presenting in an ADHD outpatient clinic. Correlational analyses were performed between neuropsychological data, clinical rating scales, and a personality-based measure. Though inattention was found to positively correlate between the two tests ($r = 0.49$, $p = 0.01$), no association with clinical measures and inattention was found for both tests. While hyperactivity did not correlate between both tests, current ADHD symptoms were positively associated with Nesplora Aquarium's motor activity ($r = 0.52$ to 0.61, $p < 0.05$) and the Qb-Test's hyperactivity ($r = 0.52$ to 0.71, $p < 0.05$). Conclusively, the overall comparability of the tests was limited and correlation with clinical parameters was low. While our study shows some interesting correlation between clinical symptoms and sub-scales of these tests, usage in clinical practice is not recommended.

Keywords: ADHD; neuropsychology; continuous performance test; Qb-Test; Nesplora Aquarium; attention; hyperactivity; GHQ-28; UPPS; impulsivity

1. Introduction

Attention deficit hyperactivity disorder (ADHD) is one of the most common neurodevelopmental disorders in childhood [1] and persists into adulthood in 40–55% of the cases [2]. The prevalence of ADHD in adults has been estimated to be 3.4% of the general population [3]. In order to diagnose ADHD in adults, a threshold of five inattention and/or five hyperactivity–impulsivity symptoms that cause clinically significant impairment in at least two functional domains of life is required in DSM-5 [4]. Adult ADHD has been associated with comorbid mental disorders such as depression, anxiety disorders, bipolar disorder, and substance use disorders [5–7] as well as non-psychiatric problems, for example obesity and traffic accidents [8,9]. Individuals with ADHD experience more functional impairment in multiple domains of life such as education, work, and risky activities [10,11]. To avoid such negative consequences, adults with ADHD require a precise diagnosis to allow specific treatment. According to the current clinical guidelines, continuous performance tests, i.e., neuropsychological tests measuring selective and sustained attention, have no role in the diagnostic process. Diagnosis of ADHD, or the exclusion thereof, should not be made solely based on neuropsychological testing. Neuropsychological testing and behavioral observation can serve a supplementary tool in the diagnostic process [12]. In the British guidelines,

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neuropsychological testing is not specifically recommended for diagnosis. Rating scales and observational data should be taken into account when there is doubt about the diagnosis [13]. ADHD is a clinical diagnosis made on the basis of the developmental background, medical history as well as former and current symptoms of patients.

Continuous performance tests (CPT) are among neuropsychological tests measuring the core symptoms of ADHD including inattention and impulsivity. Omission errors, commission errors, and hit reaction time are considered to be associated with ADHD symptoms [14–16]. However, the accuracy and usefulness of CPTs in ADHD patients are critically discussed due to their lack of sensitivity and specificity [17]. The predictive power of these measures in differentiating ADHD patients from controls, or patients with other mental disorders, is insufficient [18,19]. CPT variables and ADHD symptoms are associated only to a small amount, as only 52% of ADHD patients have correctly been classified as ADHD by using a CPT [20]. With an error rate of 80% in classifying the patients into the inattentive subtype and 23% in classifying the patients into the hyperactive subtype, the CPT was not able to correctly discriminate between the different subtypes of ADHD.

Recent findings suggest that a multidimensional approach using neuropsychological assessments in combination with other clinical measures enhances establishing an adult ADHD diagnosis [21]. An extension of conventional symptom-based classification by integrating different methods and perspectives may enable precise diagnosis, which is needed to initiate accurate treatment [22]. ADHD is a good test field for this endeavor, as neuropsychological tests offer the possibility to overcome clinical problems. Neuropsychological data provides evidence that executive functioning such as response inhibition, vigilance, working memory, and planning is impaired among patients with ADHD [23]. Nevertheless, moderate effect sizes and lack of universality speak against the hypothesis that ADHD solely arises from a deficit in executive control [23]. A role for tests of inhibitory deficits and delay aversion for a more precise definition of the clinical phenotype is proposed [24].

Recent commercial neuropsychological tests incorporated neuropsychological testing with an innovative twist. In this study we used two CPT measures including Nesplora Aquarium (Nesplora Technology and Behavior) [25] and the Quantified Behavioral Test (Qb-Test, marketed by Qbtech) [26]. The Qb-Test measures not only inattention and impulsivity but also hyperactivity with the use of an infrared camera and a reflector attached to a headband to record movements during the test. In Nesplora Aquarium [25] a virtual reality (VR) CPT, motor activity is measured through VR optical devices equipped with sensors and headphones. To improve the ecological validity of CPTs, VR CPTs have particularly been designed by providing a better representation of real-life situations [25]. Both tests are marketed by the manufacturer especially for clinicians but are currently not recommended for standard clinical routine according to guidelines. Therefore, the development of valid neuropsychological tools to assess and evaluate symptoms before and after treatment is highly important.

Several studies have compared VR measures with different commercial CPTs (Test of Variables of Attention: TOVA, Conner's CPT, Vigil CPT). Variables based on VR better differentiate between ADHD subtypes (inattentive, hyperactive/impulsive, combined) and controls than CPTs not involving VR [27]. However, only 57% of ADHD patients and controls were correctly discriminated. In a recent meta-analysis, VR CPTs have been found to better differentiate between ADHD patients and controls based on the evaluation of omission errors and hit reaction time. In comparison, commission errors showed a higher discriminant power in traditional CPTs compared to VR CPTs [16]. In another comparative study, omission errors and the number of correct responses were found to be associated with current and retrospective ADHD symptoms [14]. As the results were found in healthy students, the transferability to ADHD patients is limited and should be reviewed in a clinical sample.

To our knowledge, a head-to-head comparison of these innovative tests within one same sample has not yet been made but might have important implications for test selection and clinical routing. Therefore, in this study we evaluate Nesplora Aquarium and the Qb-Test in the diagnostic workflow with patients of our adult ADHD outpatient clinic. The first aim of the current study is to compare Nesplora Aquarium and the Qb-Test in

a within-sample comparison testing adult patients presenting to an ADHD outpatient clinic. Second, we aim to assess the ecological validity of the two CPTs (i.e., Nesplora Aquarium and Qb-Test) by correlating neuropsychological data with clinical rating scales and a personality-based measure of impulsivity.

2. Materials and Methods

2.1. Participants

The clinical sample was recruited from unselected adult patients presenting to the ADHD outpatient clinic of the Department of Psychiatry, Psychosomatic Medicine, and Psychotherapy, University Hospital Frankfurt, for diagnostic assessment of possible ADHD between May and November 2019. Among the 29 participants (Table 1), 23 (79.3%) were diagnosed with ADHD after the full clinical diagnostic assessment. Six patients (20.7%) did not meet the diagnostic criteria. Comorbid mental disorders were present in 17 (73.9%) of the ADHD patients, including depression ($n = 13$, 56.5%), substance abuse disorders ($n = 3$, 13.0%), personality disorders ($n = 2$, 8.7%) and delusional disorders ($n = 1$, 4.3%). Six patients (20.7%) did not show any other comorbid mental disorder apart from ADHD. The structured diagnostic interview for ADHD in adults (DIVA 2.0) [28] was used to assess the diagnostic criteria and identify the different subtypes of ADHD. Among the ADHD patients, one patient each (4.3%) was referred to as inattentive and hyperactive/impulsive, respectively, whereas 13 patients (56.5%) were classified as combined subtype. During the diagnostic process none of the patients was taking ADHD medication. Two patients received ADHD medication before the protocol. One patient was diagnosed with ADHD in childhood and received Ritalin, which was used for a short term. The second patient received treatment in 2011 and has used Medikinet for a period of 3 months. All other patients were treatment naive. Signed informed consent forms were obtained from the participants. The study was approved by the Ethics Committee of the University Hospital Frankfurt (Votum No. 425/14).

Table 1. Sample and test characteristics.

n	29
Demographics	
Age (M (years)) ± SD	35.24 ± 11.05
Sex	
Males	10 (34.5%)
Females	19 (65.5%)
Diagnosis	
ADHD	23 (79.3%)
Non-ADHD	6 (20.7%)
Comorbid disorders among ADHD patients	17 (73.9%)
Depression	13 (56.5%)
Substance abuse disorders	3 (13.0%)
Personality disorders	2 (8.7%)
Delusional disorders	1 (4.3%)
ADHD testing	
DIVA-ADHD subtypes among ADHD patients	
Inattentive	1 (4.3%)
Hyperactive/Impulsive	1 (4.3%)
Combined	13 (56.5%)
WRI ($n = 27$, mean, (±SD))	
Attention disorder	6.81 (±3.03)
Overactivity	3.7 (±1.82)
Temperament	2.89 (±2.29)
Affective lability	3.85 (±2.48)
Stress intolerance	3.74 (±2.19)
Disorganization	6.93 (±2.97)
Impulsiveness	5.41 (±2.1)
Total	4.76 (±1.7)
WURS-k total ($n = 26$ mean, (±SD))	36.81 (±11.23)

Table 1. *Cont.*

Psychological Questionnaires	
GHQ-28 (*n* = 25 mean, (±SD))	1.17 (±0.47)
Somatic symptoms	1.17 (±0.52)
Anxiety/insomnia	1.35 (±0.61)
Social dysfunction	1.39 (±0.53)
Severe depression	0.77 (±0.6)
UPPS (*n* = 22 mean, (±SD))	
Urgency	2.53 (±0.39)
Lack of premeditation	2.53 (±0.48)
Lack of perseverance	2.54 (±0.26)
Sensation seeking	2.56 (±0.33)
Total	2.54 (±0.15)
Neuropsychological testing	
Nesplora principal components (*n* = 29 mean, (±SD))	
Motor activity	0.00 (±1.00)
Inattention	0.00 (±1.00)
Switching	0.00 (±1.00)
Reaction time	0.00 (±1.00)
Impulsivity	0.00 (±1.00)
Qb-Test principal components (*n* = 29 mean, (±SD))	
Activity	1.95 (±1.19)
Impulsivity	1.08 (±1.01)
Inattention	0.94 (±1.17)
Nesplora variables (*n* = 29 mean, (±SD))	
Perseverative errors (*n*)	16.66 (±6.78)
Switching reaction time (mean) (ms)	−8894.12 (±2611.34)
Switching correct answers (*n*)	−16.67 (±2.72)
Total commission errors (*n*)	18.17 (±7.28)
Commission errors reaction time (mean) (ms)	747.97 (±189.27)
Commission errors reaction time (SD) (ms)	133,201.5 (±82,565.08)
Discrepancy of correct answers (*n*)	−0.121 (±3.18)
Correct answers reaction time (mean) (ms)	953.83 (±119.48)
Correct answers reaction time (SD) (ms)	98,724.49 (±35,981.23)
Sum of distance (mean)	0.2914 (±0.26)
Dual task correct answers (*n*)	119.64 (±10.34)
Total omission errors (*n*)	22.55 (±19.5)
Movement in the pitch shaft (mean)	0.10 (±0.07)
Movement in the roll shaft (mean)	0.08 (±0.08)
Movement in the yaw shaft (mean)	0.11 (±0.12)
Qb-Test variables (*n* = 29 mean, (±SD))	
Time active (>1 cm/s)	23.62 (±16.91)
Distance (m)	12.71 (±10.44)
Area (cm^2)	49.10 (±39.04)
Micro events (>1 mm)	6301.9 (±4149.57)
Motion simplicity (*n*)	44.24 (±12.34)
Total omission errors (*n*)	12.39 (±13.91)
Total commission errors (*n*)	1.74 (±1.67)
Correct answers reaction time (mean)	609.9 (±109.69)
Correct answers reaction time (SD)	177.52 (±61.35)

n = size of sample, M = mean, SD = standard deviation, ms = millisecond, cm = centimeter, s = second, m = meter, mm = millimeter, cm^2 = square centimeter. ADHD = attention deficit hyperactivity disorder, DIVA = structured diagnostic interview for ADHD in adults, WURS-k = short form of Wender-Utah Rating Scale.

2.2. Procedure

The patients were seen by experienced clinicians (O.G., N.B.-K.) to assess current and former symptoms in adulthood and childhood with the use of the structured diagnostic interview for ADHD in adults (DIVA 2.0) [28]. Childhood school records were assessed. Medical history including former substance abuse, mental disorders comorbidities, somatic disorders, and family anamnesis of ADHD were assessed. Patients were interviewed with

the Wender–Reimherr Interview (WRI) [29] by an independent trained interviewer (A.B.) and were asked to fill out the following self-report instruments: short form of the Wender–Utah Rating Scale (WURS-k, cut off for the diagnosis of a childhood ADHD sum score ≥30) [30], Impulsive Behavior Scale (UPPS) [31] and the General Health Questionnaire (GHG-28) [32]. Afterwards, neuropsychological testing took place. All patients were tested with two continuous performance tests: the Quantified Behavior Test [26] and Nesplora Aquarium [25]. Testing order was randomized across the sample.

2.3. Neuropsychology

2.3.1. Nesplora Aquarium

Nesplora Aquarium is a computerized CPT based on VR [25]. Through VR optical devices participants are immersed in a virtual aquarium. Throughout the test, visual and auditory stimuli are being presented to the patients and different tasks must be performed. There is a training task at the beginning to familiarize with the stimuli and the equipment. Through the sensors in the VR-glasses head movements are measured. After the training task, which is not included in the evaluation, two tasks are to be performed (Figure 1a,b). The test lasts about 18 min and includes training items in every task, which are not considered in the evaluation. The description of the variables measured in the test can be obtained from the Appendix B (Table A1).

2.3.2. Quantified Behavior Test

The Qb-Test [26] measures the cardinal symptoms of ADHD: inattention, impulsivity and hyperactivity in a computerized test lasting for about 20 min. The equipment consists of a headband with a reflector, which is captured by an infrared camera to measure motor activity during the test. As shown in Figure 1c visual stimuli are being presented, and the participant is supposed to press a button whenever there is an exact repetition of the prior stimulus. Whenever the stimuli are not repeated, participants are instructed to withhold pressing. The test provides raw scores of inattention (omission errors, reaction time, variation of reaction time during the second half of the test), impulsivity (commission errors, normalized commission errors) and hyperactivity (time active, distance, area, micro events, motion simplicity). The description of the variables can be obtained from the Appendix B (Table A1). Qb-Tech provides single variables as well as the three principal components of inattention, impulsivity, and hyperactivity, derived from a principal component analysis.

2.3.3. Diagnostic Interview for ADHD in adults (DIVA)

DIVA 2.0 (Diagnostic Interview for ADHD in adults) [28] is a semi-structured interview assessing the ADHD criteria based on the fourth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) [33]. The DIVA 2.0 consists of three parts that are each applicable for both childhood (before age 12) and adulthood. The first and the second parts assess the DSM-IV criteria for the core symptom clusters of ADHD including inattention and hyperactivity/impulsivity, respectively. For each criterion and age group, specific examples are provided. The third part evaluates functional impairment caused by the ADHD symptoms in five domains (including work/education, relationships and family life, social contacts, free time/hobbies, self-confidence/self-image) specifically during adulthood and childhood. Though the DIVA 2.0 is based on DSM-IV, the diagnosis was made based on the current DSM-5, whereby it applies, that symptoms are sufficient to make the ADHD diagnose.

2.3.4. Wender–Reimherr Interview (WRI)

The WRI [29] is the German adaptation of the Wender–Reimherr Adult Attention Deficits Disorders Scale (WRAADDS) [34]. The WRI is a structured interview for assessing ADHD core symptoms and other related problems in adults. The interview includes 28 questions covering seven psychopathological domains including attention deficit, hyperactivity/restlessness, temper, affective lability, emotional over-reactivity, disorganization,

and impulsivity. The questions are rated on a scale from 0 "Does not apply" to 2 "Often occurs". The WRI was used for generating a dimensional score of ADHD symptoms. The diagnosis was based on the DSM-V criteria.
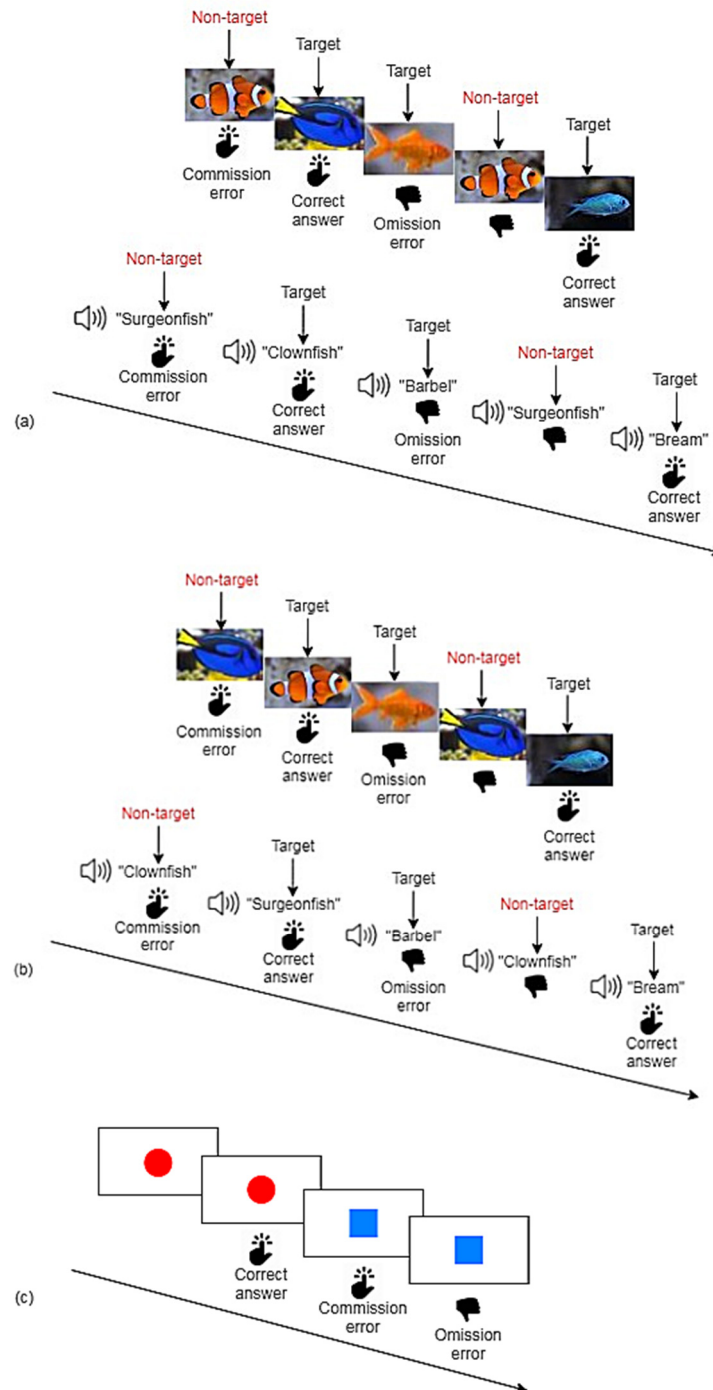
Figure 1. Schematic diagrams of Nesplora Aquarium and Qb-Test. (**a**) In the first step of Nesplora Aquarium, the participant's task is to press the button in response to all visual stimuli except for clownfish and to all auditory stimuli except for surgeonfish. (**b**) In the second step of Nesplora Aquarium, the participant is asked to press the button while observing all stimuli except for surgeonfish and while hearing all stimuli except for clownfish (inversed task). (**c**) In the Qb-Test, the participant's task is to press a button whenever an exact repetition of the prior stimulus occurs.

2.3.5. Wender–Utah Rating Scale (WURS-k)

The WURS-k [30] is a self-report measure that is used to retrospectively evaluate childhood ADHD symptoms. We used the short form comprising 25 items for discriminating patients with ADHD versus controls. The items are rated on a 5-point response scale ranging from 0 "Not at all" to 4 "Very much". A total score of 30 is considered as a cutoff to diagnose ADHD in childhood [35].

2.3.6. UPPS Impulsive Behavior Scale (UPPS)

The UPPS [31] is a self-report measure consisting of 45 items that are rated on a 4-point Likert scale ranging from 1 (strongly agree) to 4 (strongly disagree). The UPPS includes four subscales: urgency, lack of premeditation, lack of perseverance, and sensation seeking. In a psychometric study of the German adaptation of the UPPS in a German-speaking sample [36], exploratory and confirmatory factor analyses showed a four-factor structure similar to the results in the original study. The four subscales showed a very good internal consistency with Cronbach's alpha ranging from 0.80 to 0.85 [36].

2.3.7. General Health Questionnaire-28 (GHQ-28)

The GHQ-28 [32] was developed to assess emotional distress and consists of 28 items, with four subscales including somatic symptoms, anxiety/insomnia, social dysfunction, and severe depression. The items can be scored from 0 to 3.

2.4. Data Analysis

To enable a comparison between the principal components of the Qb-Test and equivalent parameters of Nesplora Aquarium, a principal component analysis was performed on the variables of Nesplora Aquarium. Based on the description of the measures provided by Nesplora Aquarium [25], the 15 named variables (described in Appendix B, Table A1) were included. A varimax rotation was used as the factors were expected to be independent. Item loadings below 0.30 were not considered. The scree plot can be found in the Appendix A (Figure A1). The correlation matrix was nonpositive definite, which means that some of the eigenvalues are not positive values. In this case the Kaiser-Meyer-Olkin measure and Bartlett test cannot be calculated. Eigenvalues were calculated for each factor in the data, whereas five factors had eigenvalues over Kaiser's criterion of 1. The initial eigenvalues explained in sum 89.85% of variance. The factor loadings after rotation can be obtained from Table 2.

Table 2. Rotated Factor Loadings.

	Rotated Factor Loadings				
	Motor Activity	**Inattention**	**Switching**	**Reaction Time**	**Impulsivity**
Sum of distance (mean)	0.98				
Movement in the yaw shaft (mean)	0.96				
Movement in the pitch shaft (mean)	0.95				
Movement in the roll shaft (mean)	0.93				
Total omission errors (*n*)		0.95			
Dual task correct answers (*n*)		−0.92			
Correct answers reaction time (SD) (ms)		0.92			
Commission errors reaction time (SD) (ms)		0.73		0.49	
Perseverative errors (*n*)		0.67	0.31		0.48
Switching reaction time (mean) (ms)			0.91		
Switching correct answers (*n*)		0.31	0.87		
Discrepancy of correct answers (*n*)		0.41	−0.73		
Commission errors reaction time (mean) (ms)				0.89	
Correct answers reaction time (mean) (ms)				0.80	
Total commission errors (*n*)					0.95

n = number of, ms = millisecond.

The variables that highly load on factor 1 ("Sum of distance (mean)", "Movement in the yaw shaft (mean)", "Movement in the pitch shaft (mean)", "Movement in the roll shaft (mean)") are measures of movement, implicating that factor 1 represents "Motor activity". Factor 1 explains 36.62% of variance. The second factor "Inattention" is formed by 5 variables that loaded highest on this factor ("Total omission errors (*n*)", "Dual task correct answers (*n*)", "Correct answers reaction time (SD) (ms)", "Commission errors reaction time (SD) (ms)", "Perseverative errors (*n*)") and explains 22.57% variance. The three variables that cluster on the third factor "Switching" are represented by the reaction time of hits and the total number of hits ("Switching reaction time (mean)", "Switching correct answers (*n*)") as well as by the "Discrepancy of correct answers (*n*)". 13.04% variance can be explained by factor 3. Factor 4 "Reaction time" is represented by "Commission errors reaction time (mean) (ms)" and "Correct answers reaction time (mean) (ms)" and explains 10.53% variance. The last factor 5 is formed by only one variable namely "Total commission errors (*n*)". The 7.08% variance is explained by factor 5 "Impulsivity". The factors were included in the correlational analyses with the principal components of the Qb-test. To test the comparability of the two CPTs, correlational analyses were performed. Before, differences in means and standard deviations were calculated (Table 1). We then correlated the five principal components of Nesplora Aquarium derived from the principal component analysis with the three principal components of the Qb-Test, which have previously been calculated and provided by Qbtech (Table 3). To enable a more detailed insight in the particular relationships between the single variables, all variables of Nesplora Aquarium and the Qb-Test, that formed the principal components, were correlated. In a last step correlational analyses were performed to assess the compatibility of the two CPTs with clinical measures. Firstly, the principal components of both CPTs and secondly all variables provided by the CPTs were correlated with clinical rating scales (WRI, WURS-k, GHQ-28) and the personality-based measure (UPPS). The analyses were run with IBM SPSS Statistics (IBM Corp. Released 2017. IBM SPSS Statistics for Macintosh, Version 25.0. Armonk, NY: IBM Corp.) [37]. Although this was an exploratory study on a highly specific, small sample of ADHD patients, we additionally corrected for multiple testing when necessary. Because of the high collinearity of our variables, we calculated the number of independent tests as done previously [38,39]. We calculated the principal components explaining 90% variance for each table to estimate the effective number of independent tests performed in our correlational analyses (Tables 4–6). Afterwards, the Bonferroni correction formula was used to calculate the adjusted significance levels, as proposed [39]: $0.05/8 = ^{\dagger} p = 0.006$ (Table 4); $0.05/9 = ^{\dagger} p = 0.006$ (Table 5); $0.05/10 = ^{\dagger} p = 0.005$ (Table 6).

3. Results

Partial correlations (controlling for sex, age, and order of test administration) were carried out between the principal components of Nesplora Aquarium and the Qb-Test. A significant positive correlation was found between the inattention factors of Nesplora Aquarium and the Qb-Test ($r = 0.49$, $p = 0.01$) (Table 3).

Table 3. Correlations between the principal components of Nesplora Aquarium and the Qb-Test.

	Qb-Test		
	Hyperactivity	**Impulsivity**	**Inattention**
Nesplora Aquarium	*r*	*r*	*r*
Motor activity	0.23	−0.29	0.28
Inattention	0.26	−0.02	0.49 *
Switching	0.26	0.23	−0.25
Reaction time	−0.22	−0.21	−0.35
Impulsivity	0.06	0.04	−0.007

* $p < 0.05$.

To further specify the relation between the two continuous performance tests, partial correlations (controllin1.g for sex, age, and order of test administration) between the underlying variables of the principal components of Nesplora Aquarium and the Qb-Test were performed. Highly significant correlations were found especially among the inattention variables of the Qb-Test, correlating with variables of Nesplora Aquarium (Table 4): Omission errors as well as correct answers reaction time (SD), indicating sustained attention or fatigability, positively correlated between both tests ($r = 0.58$ and 0.52, respectively, $p = 0.002$ and 0.006, respectively). Omission errors in the Qb-Test negatively correlated with working memory, measured by "dual task correct answers" in Nesplora Aquarium ($r = -0.53$, $p = 0.006$), whereby low scores indicate deficits in working memory. Furthermore, omission errors (Qb-Test) were associated with movement, measured by Nesplora Aquarium ("movement in the roll shaft") ($r = 0.53$, $p = 0.006$). All associations described were highly significant under the corrected significance value of $p < 0.006$ after adjusting for multiple testing.

In a next step neuropsychological data was analyzed regarding the compatibility with clinical measures. Table 5 shows partial correlations (controlling for sex, age, and order of test administration) between the principal components of Nesplora Aquarium and the Qb-Test with the WRI, WURS-k, UPPS, and GHQ-28. Among all clinical parameters, the WRI was found to be related mostly to neuropsychological data, whereby two correlations were highly significant: affective lability in the WRI negatively correlated with impulsivity in Nesplora Aquarium ($r = -0.62$, $p = 0.008$), and overactivity in the WRI showed a positive correlation with hyperactivity in the Qb-Test ($r = 0.71$, $p = 0.001$). A positive significant correlation was found between WURS-k and hyperactivity in the Qb-Test ($r = 0.50$, $p = 0.04$). The urgency subscale of the UPPS negatively correlated with impulsivity in the Qb-Test ($r = -0.49$, $p = 0.046$). No significant correlations were found between the GHQ-28 and neuropsychological measures. The described positive correlation between overactivity in the WRI and hyperactivity in the Qb-Test showed to be highly significant after correction for multiple testing ($p < 0.006$).

In a closer examination of the relations between neuropsychological data and clinical measures, partial correlations (controlling for sex, age, and order of test administration) between the underlying variables of the principal components of Nesplora Aquarium and the Qb-Test with the WRI, WURS-k, UPPS, and GHQ-28 were carried out (Table 6). In line with the previous results, the WRI showed the most significant correlations with the continuous performance tests: Overactivity in the WRI negatively associated with discrepancy of correct answers ($r = -0.63$, $p = 0.007$) in Nesplora Aquarium while it positively correlated with area, which measures movement in the Qb-Test ($r = 0.63$, $p = 0.007$). Attention disorder in the WRI correlated positively with motion simplicity in the Qb-Test (0.64, $p = 0.005$). The correlation revealed to be highly significant after correction of multiple testing ($p < 0.005$). The total WRI score was positively associated with movement in Nesplora Aquarium ($r = 0.61$, $p = 0.009$).

Table 4. Correlations between the underlying variables of the principal components of Nesplora Aquarium and the Qb-Test.

	Qb-Test									
	Hyperactivity					Inattention			Impulsivity	
	Time Active (>1 cm/s)	Distance (m)	Area (cm^2)	Micro Events (>1 mm)	Motion Simplicity (n)	Omission Errors (n)	Correct Answers Reaction Time (mean)	Correct Answers Reaction Time (SD)	Commission Errors (n)	Normalized Commission Errors (n)
Nesplora Aquarium										
Perseveration errors (n)	0.12	0.14	0.23	0.15	0.40 *	0.41 *	−0.05	0.22	−0.21	−0.20
Switching reaction time (mean) (ms)	0.18	0.28	0.29	0.23	0.03	0.03	−0.36	−0.009	0.14	0.13
Switching correct answers (n)	0.26	0.26	0.28	0.28	0.19	0.11	−0.27	0.02	0.15	0.16
Total commission errors (n)	0.18	0.10	0.16	0.16	0.27	0.05	−0.08	0.12	0.14	0.14
Total omission errors (n)	0.08	0.18	0.24	0.13	0.39	0.58 **,†	0.27	0.50 *	−0.03	0.03
Commission errors reaction time (mean) (ms)	−0.38	−0.41 *	−0.41 *	−0.41 *	−0.38	−0.02	−0.34	−0.28	−0.20	−0.19
Commission errors reaction time (SD) (ms)	−0.03	0.03	0.13	0.02	0.36	0.33	0.07	0.17	−0.23	−0.21
Correct answers reaction time (mean) (ms)	−0.11	−0.11	−0.09	−0.11	−0.02	−0.04	−0.12	−0.19	−0.25	−0.26
Correct answers reaction time (SD) (ms)	0.03	0.09	0.17	0.06	0.43 *	0.48 *	0.38	0.52 **,†	0.15	0.19
Discrepancy of correct answers (n)	−0.36	−0.27	−0.32	−0.34	−0.19	0.18	0.42 *	0.35	0.23	0.26
Dual task correct answers (n)	−0.13	−0.19	−0.27	−0.17	−0.44 *	−0.53 **,†	−0.21	−0.48 *	−0.02	−0.08
Sum of distance (mean)	0.10	0.08	0.17	0.12	0.38	0.46 *	0.14	0.20	−0.08	−0.05
Movement in the pitch shaft (mean)	0.11	0.07	0.15	0.13	0.35	0.35	0.01	0.08	−0.10	−0.06
Movement in the roll shaft (mean)	0.08	0.04	0.13	0.09	0.36	0.53 **,†	0.17	0.18	−0.20	−0.17
Movement in the yaw shaft (mean)	0.09	0.11	0.20	0.12	0.38	0.45 *	0.18	0.27	0.02	0.06

n = number of, SD = standard deviation, ms = millisecond, cm = centimeter, s = second, m = meter, mm = millimeter, cm^2 = square centimeter. ** $p < 0.01$. * $p < 0.05$. † $p < 0.006$.

Table 5. Correlations between the principal components of Nesplora Aquarium and the Qb-Test with WRI, WURS-k, UPPS, and GHQ-28.

	WRI									Total WURS-k
	Attention Disorder	Overactivity	Temperament	Affective Lability	Stress Intolerance	Disorganization	Impulsiveness	TOTAL		
Nesplora Aquarium										
Motor activity	0.25	0.52 *	0.36	0.61 *	0.32	0.30	0.53 *	0.58 *		−0.08
Inattention	0.48	0.08	−0.17	0.22	0.40	0.30	0.30	0.34		0.33
Switching	0.41	0.56 *	0.37	0.39	−0.02	0.08	−0.03	0.34		0.06
Reaction time	−0.36	0.12	0.26	0.03	0.008	−0.15	−0.18	−0.07		0.10
Impulsivity	−0.14	−0.32	−0.46	−0.62 **	−0.34	−0.36	−0.17	−0.50 *		−0.32
QB-Test										
Hyperactivity	0.45	0.71 **,†	0.52 *	0.47	0.20	−0.02	0.47	0.54 *		0.50 *
Impulsivity	0.34	−0.22	−0.46	−0.21	0.08	0.37	−0.08	−0.003		−0.09
Inattention	0.28	−0.29	−0.42	0.02	0.37	0.20	0.13	0.09		0.16

	UPPS						GHQ−28				
	Urgency	Lack of Premeditation	Lack of Perseverance	Sensation Seeking	Total		Somatic Symptoms	Anxiety/Insomnia	Social Dysfunction	Depression	Total
Nesplora Aquarium											
Motor activity	0.15	−0.09	0.08	0.16	0.14		−0.14	0.03	0.06	−0.001	−0.01
Inattention	−0.37	0.15	0.07	0.02	−0.05		0.20	0.18	0.12	−0.01	0.15
Switching	0.32	−0.45	−0.41	0.17	−0.24		0.12	0.23	0.42	−0.11	0.21
Reaction time	0.04	−0.18	0.19	0.03	−0.03		0.21	0.41	0.23	0.39	0.39
Impulsivity	0.08	0.27	−0.05	−0.46	−0.03		0.13	−0.19	−0.02	0.33	0.06
QB-Test											
Hyperactivity	0.44	−0.44	−0.27	0.25	−0.06		0.28	0.44	0.46	0.15	0.42
Impulsivity	−0.49 *	0.04	0.07	−0.13	−0.28		−0.20	−0.28	−0.23	−0.07	−0.24
Inattention	−0.44	0.48	0.34	−0.12	0.19		−0.32	−0.19	−0.13	−0.31	−0.29

WRI = Wender–Reimherr Interview, WURS-k = Wender–Utah Rating Scale, UPPS = UPPS Impulsive Behavior Scale, GHQ-28 = General Health Questionnaire-28. ** $p < 0.01$. * $p < 0.05$. † $p < 0.006$.

Table 6. Correlations of the underlying variables of the principal components of Nesplora Aquarium and the Qb-Test with WRI, WURS-k, UPPS, and GHQ-28.

	WRI								
	Attention Disorder	Overactivity	Temperament	Affective Lability	Stress Intolerance	Disorganization	Impulsiveness	Total	Total WURS-k
Nesplora Aquarium									
Perseveration errors (n)	0.50 *	0.52 *	0.11	0.33	0.21	0.09	0.14	0.38	0.29
Switching reaction time (mean) (ms)	0.50 *	0.55 *	0.25	0.43	0.03	0.19	−0.03	0.39	0.009
Switching correct answers (n)	0.48	0.45	0.19	0.27	0.02	0.13	0.11	0.33	0.1
Total commission errors (n)	0.11	−0.11	−0.39	−0.38	−0.17	−0.21	0.08	−0.22	−0.29
Total omission errors (n)	0.50 *	0.12	−0.08	0.33	0.42	0.37	0.37	0.43	0.25
Commission errors reaction time (mean) (ms)	−0.50 *	−0.20	0.01	−0.22	−0.08	−0.16	−0.33	−0.30	−0.10
Commission errors reaction time (SD) (ms)	0.21	0.37	0.29	0.50 *	0.48	0.17	0.28	0.46	0.35
Correct answers reaction time (mean) (ms)	−0.29	0.11	0.19	0.01	0.02	−0.08	−0.10	−0.04	0.26
Correct answers reaction time (SD) (ms)	0.35	−0.05	−0.26	−0.005	0.26	0.19	0.18	0.15	0.26
Discrepancy of correct answers (n)	−0.22	−0.63 **	−0.60 *	−0.43	0.04	0.08	−0.04	−0.34	−0.02
Dual task correct answers (n)	−0.56 *	−0.09	0.21	−0.22	−0.38	−0.32	−0.42	−0.38	−0.17
Sum of distance (mean)	0.42	0.53 *	0.24	0.58 *	0.33	0.36	0.53 *	0.61 *	−0.07
Movement in the pitch shaft (mean)	0.36	0.43	0.28	0.53 *	0.28	0.34	0.54 *	0.56 *	−0.18
Movement in the roll shaft (mean)	0.38	0.60 *	0.32	0.54 *	0.24	0.18	0.58 *	0.56 *	0.06
Movement in the yaw shaft (mean)	0.44	0.53 *	0.17	0.59 *	0.39	0.42	0.46	0.61 **	−0.05
Qb−Test									
Time active (>1 cm/s)	0.27	0.55 *	0.42	0.18	−0.10	−0.04	0.26	0.29	0.45
Distance (m)	0.51 *	0.58 *	0.42	0.33	0.06	0.19	0.3	0.48	0.58 *
Area (cm^2)	0.60 *	0.63 **	0.44	0.38	0.09	0.17	0.31	0.52 *	0.55 *
Micro events (>1 mm)	0.4	0.61 *	0.48	0.29	−0.02	0.06	0.32	0.41	0.53 *
Motion simplicity (n)	0.64 **,†	0.45	0.44	0.41	0.25	−0.07	0.39	0.49 *	0.38
Omission errors (n)	0.28	0.07	−0.27	0.23	0.47	0.22	0.35	0.29	0.37
Correct answers reaction time (mean) (ms)	0.02	−0.37	−0.38	−0.13	0.22	−0.02	0.22	−0.08	0.24
Correct answers reaction time (SD) (ms)	0.3	−0.22	−0.35	0.04	0.37	0.35	0.11	0.15	0.26
Commission errors (n)	0.26	−0.23	−0.34	−0.18	0.07	0.32	0.06	0.02	0.03
Normalized commission errors(n)	0.26	−0.26	−0.39	−0.17	0.11	0.34	0.12	0.03	0.04

Table 6. *Cont.*

	UPPS					GHQ-28				
	Urgency	Lack of Premeditation	Lack of Perseverance	Sensation Seeking	Total	Somatic Symptoms	Anxiety/ Insomnia	Social Dysfunction	Depression	Total
Nesplora Aquarium										
Switching correct answers (*n*)	0.16	−0.32	−0.34	0.08	−0.25	0.07	0.22	0.39	0.09	0.24
Total commission errors (*n*)	0.06	0.25	−0.12	−0.40	−0.05	0.13	−0.17	0.02	0.26	0.06
Total omission errors (*n*)	−0.35	0.12	−0.05	−0.01	−0.13	0.18	0.2	0.1	−0.08	0.13
Commission errors reaction time (mean) (ms)	−0.10	0.02	0.33	−0.08	0.04	0.12	0.22	0.12	0.43	0.27
Commission errors reaction time (SD) (ms)	−0.18	−0.07	0.21	0.17	0.02	0.23	0.46	0.3	0.13	0.35
Correct answers reaction time (mean) (ms)	−0.01	−0.19	0.13	0.08	−0.06	0.21	0.38	0.09	0.27	0.3
Correct answers reaction time (SD) (ms)	−0.38	0.18	0.16	0.05	0.02	0.22	0.14	0.17	0.23	0.23
Discrepancy of correct answers (*n*)	−0.41	0.53 *	0.47	−0.11	0.3	−0.24	−0.43	−0.51 *	−0.08	−0.39
Dual task correct answers (*n*)	0.34	−0.21	0.09	0.15	0.15	−0.24	−0.15	−0.11	0.001	−0.16
Sum of distance (mean)	0.13	−0.06	0.04	0.15	0.12	−0.15	−0.04	0.08	−0.06	−0.05
Movement in the pitch shaft (mean)	0.11	−0.02	−0.02	0.1	0.09	−0.08	−0.007	0.09	0.03	0.01
Movement in the roll shaft (mean)	0.33	−0.11	−0.06	0.16	0.16	−0.006	0.06	0.12	0.05	0.07
Movement in the yaw shaft (mean)	0.02	−0.08	0.13	0.17	0.1	−0.24	−0.09	0.05	−0.15	−0.13
Qb−Test										
Time active (>1 cm/s)	0.50 *	−0.51 *	−0.39	0.28	−0.11	0.31	0.36	0.3	0.21	0.37
Distance (m)	0.43	−0.42	−0.30	0.38	0.01	0.1	0.22	0.09	−0.22	0.07
Area (cm^2)	0.43	−0.40	−0.29	0.37	0.02	0.14	0.27	0.09	−0.20	0.1
Micro events (>1 mm)	0.52 *	−0.49 *	−0.36	0.34	−0.04	0.23	0.33	0.23	0.04	0.26
Motion simplicity (*n*)	0.26	−0.11	−0.22	0.13	0.05	0.3	0.42	0.23	0	0.3
Omission errors (*n*)	−0.34	0.21	0.37	−0.06	0.09	−0.21	0.1	−0.04	0.04	−0.03
Correct answers reaction time (mean) (ms)	−0.34	0.4	0.26	−0.10	0.16	−0.31	−0.17	−0.17	−0.13	−0.24
Correct answers reaction time (SD) (ms)	−0.51 *	0.22	0.22	0.02	−0.01	−0.21	−0.19	−0.17	−0.38	−0.29
Commission errors (*n*)	−0.40	0.03	0.03	0.03	−0.16	−0.21	−0.35	−0.25	−0.19	−0.31
Normalized commission errors(*n*)	−0.47	0.09	0.04	−0.02	−0.19	−0.24	−0.33	−0.27	−0.17	−0.32

WRI = Wender–Reimherr Interview, WURS-k = Wender–Utah Rating Scale, UPPS = UPPS Impulsive Behavior Scale, GHQ-28 = General Health Questionnaire-28. *n* = number of, SD = standard deviation, ms = millisecond, cm = centimeter, s = second, m = meter, mm = millimeter, cm^2 = square centimeter. * $p < 0.05$. ** $p < 0.01$. † $p < 0.005$.

4. Discussion

The current study aimed to compare Nesplora Aquarium and the Qb-Test in a within-sample comparison of adult patients presenting to our ADHD outpatient clinic and related test measures to clinical scores. The ecological validity of the two CPTs (i.e., Nesplora Aquarium and Qb-Test) was assessed regarding the correlation with clinical rating scales (WRI, WURS-k, GHQ-28) and a personality-based measure (UPPS). The overall comparability of the tests was limited. Despite the congruent measure of inattention in both tests, no correlation with clinical features was found. While hyperactivity positively associated with current ADHD symptoms in both tests, in the Qb-Test it additionally reflected childhood ADHD symptoms. Impulsivity was shown to be represented independently by both tests and poorly associated with clinical measures and UPPS. We did not only investigate a previously described component structure of the Qb-test, but we also calculated the varimax-rotated principal component analysis of the Nesplora Aquarium test to better compare basic components of both tests.

The factor inattention was found to positively associate between the two CPTs in a moderate way. A closer look at the variables, which define the factor inattention, confirms this finding. Omission errors and the variation of reaction time, indicating consistency of attention and fatigability, were correlated in both tests. Not surprisingly, inattention is the most basic bottleneck of both tests. While both tests seem to be well designed in assessing the feature, inattention in the tests does not have strong relations with clinical parameters.

Nesplora Aquarium provides the additional measure of working memory, defined by the parallel processing of two sensory modalities during test performance. Working memory was found to be negatively associated with omission errors in the Qb-Test, indicating that inattention is associated with significant impairment in the working memory.

Perseverative errors are another new variable of Nesplora Aquarium measuring deficits in cognitive flexibility. It was found to positively correlate with omission errors in the Qb-Test. The present findings indicate that inattention is diversely captured by CPTs, especially by Nesplora Aquarium.

We did not detect other overlaps between major components of the two tests. The correlational analyses of the underlying variables measuring hyperactivity and impulsivity did not present consistent findings, respectively. The variables of movement among the two tests did not correlate.

In the present study, 79.3% of the patients that presented to the outpatient clinic were finally diagnosed with ADHD. Apart from assessing the diagnostic accuracy of CPTs as done by a range of authors [16,17], our study allows a more complex look at the various features of ADHD, captured by clinical rating scales and a personality-based measure, and how well they are represented through neuropsychological testing. For this purpose, we evaluated the relationship of the CPTs with clinical measures including WRI for assessing ADHD symptoms in adulthood, WURS-k for a retrospective assessment of ADHD symptoms during childhood, UPPS for measuring impulsivity, and GHQ-28 for identifying relationships with short-term psychiatric disorders. In the following the results concerning the ecological validity of the CPTs will be reported for inattention, hyperactivity and impulsivity, respectively.

The factor inattention in both Nesplora Aquarium and the Qb-Test did not show any relationship with clinical rating scales or UPPS. The same applies to the factor reaction time in Nesplora Aquarium. The lack of clinical relevance of inattention is surprising, since inattention is the most consistent factor across paradigms. Also, the strong and reasonable correlations of the underlying variables measuring inattention in both tests gave reason to expect significant clinical correlates. In contrast to our findings, previous studies found low attention performance (omission errors and number of correct answers) measured by Nesplora Aquarium to positively correlate with current and retrospective ADHD symptoms [14]. In a study on the role of objective measures in assessing ADHD symptoms in children and adults [40], the inattention factor of the Qb-Test positively correlated with the inattention subscale of the Conner's ADHD rating scales-observer

ratings (CAARS-O) in adults. Nevertheless, the similar metric profile of omission errors, commission errors and hit reaction time in VR and non-VR tests is not able to affect the ecological validity just by adapting the test environment to a more real-world situation [16].

Measures of movement in the Qb-Test were found to associate with commission errors in Nesplora Aquarium, a measure of impulsivity. Variables indicating movement in Nesplora Aquarium most likely related to omission errors in the Qb-Test, a measure of inattention. A possible explanation for the lack of correlation between the activity variables of the two CPTs is that they measure movement in two different ways. In the Qb-Test, the participant's movements are recorded by using an infrared system tracking a reflective indicator located on the headband participants wear [41]. However, in Nesplora Aquarium, head movements of the participants are recorded by sensors placed in the glasses [27]. Movement might be a factor, which is not independent of the task but closely related to cognitive demands. Putting constraints to head movement (like balancing VR glasses) might impact on cognitive capabilities itself [42].

Although hyperactivity did not show significant correlation in the CPTs, a positive association with overactivity, a subscale of the WRI, was found in both tests. These findings apply for the hyperactivity factor in both CPTs as well as the underlying variables of hyperactivity in Nesplora Aquarium and the Qb-Test. These results are supported by the finding that ADHD patients show significant higher activity than patients without ADHD [19]. While the hyperactivity factors of both tests are independent, they nevertheless seem to be related to one of the most valid clinical symptom components. The additional correlations of hyperactivity with several other subscales of the WRI (overactivity, affective lability, impulsiveness for Nesplora Aquarium; overactivity and temperament for Qb-Test) indicate that hyperactivity adequately represents current symptoms of ADHD. Interestingly, affective lability, an often dismissed core symptom of adult ADHD was indexed by Nesplora Aquarium's movement parameters while it was not detected by Qb-Test's variables. The fact that Nesplora Aquarium is the more demanding and complex test, which can lead to frustration, could explain this finding. Accordingly, we assume that patients with higher affective lability show more motor activity during such tests involving a high frustration potential. Besides, affective lability is ignored by the DSM-V criteria for adult ADHD although it represents a highly important negative part in daily life of patients.

Moreover, childhood ADHD symptoms captured by the WURS-k are linked to hyperactivity in the Qb-Test. In line with our findings, hyperactivity was found to be associated with current and retrospective ADHD symptoms in another study [43]. The findings suggest that hyperactivity measured in neuropsychological testing represents the most accurate correlate of ADHD symptoms.

Impulsive decision-making might be a basic feature for measuring ADHD. However, Qb-Test's factor impulsivity, which is mainly driven by commission errors in the Qb-Test did not correlate with measures of impulsivity in Nesplora Aquarium at all, questioning whether there is a homogenous impulsivity construct across neuropsychological tests and clinical symptoms. Impulsive behavior can be differentiated into several distinct and heterogenous subtypes [44]. Moreover, impulsivity is not consistent throughout patient populations, but takes various forms according to different psychiatric disorders [45]. In the current study, impulsivity measured by the Qb-Test negatively correlated with urgency, a subscale of the UPPS. Impulsivity in Nesplora Aquarium did not show any association with the UPPS, but was negatively linked to affective lability, a subscale of the WRI. ADHD patients with high affective lability might be more afraid to make mistakes and withhold pressing rather than falsely reacting to a non-target stimulus. The positive correlation between affective lability and commission errors reaction time (SD) additionally emphasizes the variance present in both affective lability, by its definition, and commission errors reaction time. This leads to the assumption that high affective lability in ADHD patients is associated with great variability in pressing or withholding, expressed by higher motor activity driven by frustration, as mentioned above, respectively.

While sensation seeking, a subscale of the UPPS, is discussed as one of the most prominent traits of ADHD, none of the test measures of Qb-Test or Nesplora Aquarium captured this trait in patients. The lacking correlation of the total UPPS score with any of the test parameters of both CPTs emphasizes the idea that ADHD symptoms are not simply about the trait impulsivity. The CPTs showed no significant correlation with the impulsiveness subscale of the WRI. Neither subscales of the UPPS nor impulsiveness in the WRI related to commission errors in any of the CPTs. The independence of the impulsivity factors of both CPTs as well as their poor association with measures of impulsivity through clinical measures and UPPS underlines the difficulty to narrow impulsivity to a uniform construct. Our findings support the idea that behavioral components and self-reported impulsivity are largely independent [46].

The findings concerning the GHQ-28 indicate that both CPTs seem to be very specific for ADHD symptoms, as the GHQ-28 captures more general emotional distress symptoms and was almost not correlated with test measurements.

Some limitations of the study should be acknowledged. The small sample size is a limiting factor in generalizing the results on a clinical level. Making recommendations about the superiority of one of the tests in predicting specific ADHD-related symptoms would require larger study samples including control groups. However, for a within-subject repeated measure study, the sample size is comparable to that of other method comparison studies. As the sample mainly consisted of ADHD patients including a control group would be of interest. 73.9% of the patients showed comorbid disorders including depression, substance abuse disorders, personality disorders and delusional disorders. Exploring the results, taking into account the comorbidities, would be of interest for future research. However, in our study the comorbidities were not evenly distributed and our sample was small, so we were not able to study them systematically. Though this study was an exploratory analysis, correction for multiple testing was applied when necessary. Most of the highly significant correlations found proved to be significant after the applied corrected significance threshold. Further studies are needed to confirm our findings in a larger data set. Apart from these limitations, our study has some unique features: We used two commercially available continuous performance tests to measure the core symptoms of ADHD. Both tests are outstanding in terms of their technology: They make it possible to capture aspects of ADHD, which are ignored by classical paper-and-pencil-tests. The Qb-Test measures hyperactivity with the use of an infrared camera and a reflector attached to a headband to record movements during the test. During the test of Nesplora Aquarium, participants are immersed in a virtual aquarium, while motor activity is measured through VR optical devices equipped with sensors and headphones. We evaluated Nesplora Aquarium and the Qb-Test in the diagnostic workflow with patients of our adult ADHD outpatient clinic, providing highly specific results. Additionally, the factor structure of Nesplora Aquarium has to our knowledge not yet been examined by other studies and represents a new finding in the current paper.

5. Conclusions

Taken together, the current study enables a good comparison of the two CPTs and reveals detailed information on their compatibility with clinical measures. Inattention, mainly driven by test performance, is a basic factor, which overlaps between the two tests in each subject. As it fails to predict clinical parameters, this highlights the previously described problem in linking subjective and objective methods in diagnosing ADHD [19]. A very interesting test parameter is hyperactivity, which reflects current ADHD symptoms in both tests, while in the Qb-Test it is additionally associated with childhood ADHD symptoms. As there are only few findings about the compatibility of Nesplora Aquarium with clinical measures of current and childhood ADHD symptoms at this time, this issue should be addressed by further studies. Not surprisingly, both tests are linked together by the component inattention. However, as this measurement of basic test performance does not seem to have a clinical representation, we would currently not use either test as a step in the diagnostic workflow. The current findings

question the simple use of so-called objective measures in clinical ADHD diagnosis because of questionable validity. The findings emphasize the need for a new approach in diagnosis in the sense of precision medicine, going beyond conventional classification systems to enable suitable individual solutions for diagnosis and treatment [22]. While Kapur [47] asked for cognitive tests that distinguish a broad clinical phenotype into distinct treatment-relevant subgroups, our findings illustrate that such cognitive tests are hard to establish. Though continuous performance tests are intended to improve diagnosis, the current test's validity is not clearly established. For example, impulsivity measures in both tests do not correlate with clinical parameters related to ADHD impulsivity. Movement-related parameters during complex cognitive tests show some promise and should be validated in future research in deeply phenotyped samples.

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Institutional Review Board Statement: The study was reviewed and approved by the Ethics Committee of the Medical Faculty, University Hospital, Goethe University Frankfurt am Main, Frankfurt, Germany (Votum No. 425/14).

Informed Consent Statement: Informed consent was obtained from all subjects involved in the study.

Data Availability Statement: All datasets generated for this study are included in the article.

Conflicts of Interest: S.K.S. and A.R. have received speaker's and authors honoraria from Medice Arzneimittel Pütter GmbH & Co KG. and Takeda/Shire. O.G. has received speaker's honoraria from Medice Arzneimittel Pütter GmbH & Co KG. The other authors declare no conflict of interest. The funders had no role in the design of the study; in the collection, analyses, or interpretation of data; in the writing of the manuscript, or in the decision to publish the results.

Appendix A
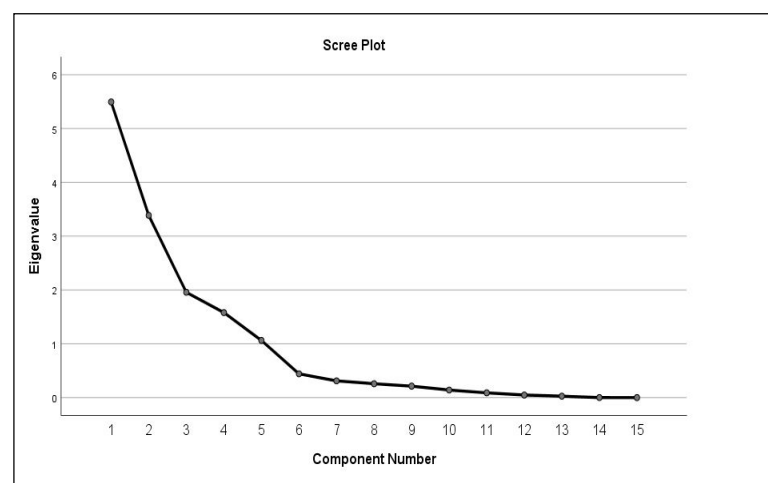
Figure A1. Scree plot of the principal component analysis. *n* = 29.

Appendix B

Table A1. Description of Variables of Nesplora Aquarium and Qb-Test.

Variables	Description
Nesplora Aquarium	
Perseverative errors (*n*)	Deficit in cognitive flexibility:
	Measured by the errors occurring when falsely continuing to respond to the previous instructions of the last task instead of following the instructions of the next task
Switching reaction time (mean) (ms)	Suffering of reaction speed while adapting to a new task:
	Measured by the difference between the reaction time of correct answers in the last part of a task with the reaction time of correct answers in the beginning of the following task
Switching correct answers (*n*)	Suffering of task execution while adapting to a new task:
	Measured by the difference between the number of correct answers in the last part of a task with the number of correct answers in the beginning of the following task
Total commission errors (*n*)	Indicator of Impulsivity:
	Measured by errors occured when participant falsely reacts to non-target stimulus
Total omission errors (*n*)	Indicator of Inattention:
	Measured by errors occured when participant fails to react to target stimulus
Commission errors reaction time (mean) (ms)	Additional information on cause of commission errors:
	Measured by time passed until the button is falsely pressed on a non-target stimulus
	Higher scores represented by low reaction time are considered to indicate higher impulsivity and/or hyperactivity
Commission errors reaction time (SD) (ms)	Indicator of variability of reaction time in commission errors:
	Measured by standard deviation of reaction time
Correct answers reaction time (mean) (ms)	Indicator of processing speed:
	Measured by the time passed since the target stimulus is presented until the button is pressed
Correct answers reaction time (SD) (ms)	Indicator of sustained attention/fatigability:
	Measured by standard deviation of reaction time
Discrepancy of correct answers (*n*)	Additional measure of consistency/fatigability:
	Measured by the difference of correct answers in the first half of a task and the correct answers in the second half of a task
Dual task correct answers (*n*)	Indicator of Working Memory:
	Measured by the correct answers in visual and auditory target stimuli by parallel processing of sensory modalities
	Inverse interpretation: high scores indicate a good working memory performance
Sum of distance (mean)	Indicator of Movement:
	Measured by the sum of movement in pitch, roll and yaw shaft
Movement in the pitch shaft (mean)	Indicator of Movement in the pitch shaft
Movement in the roll shaft (mean)	Indicator of Movement in the roll shaft
Movement in the yaw shaft (mean)	Indicator of Movement in the yaw shaft

Table A1. *Cont.*

Variables	Description
	Qb-Test
Time active	Indicator of Movement:
	Measured whenever participant moves more than 1 cm/s
Distance	Indicator of Movement:
	Measured by the reflective marker on the headband (in metres)
Area	Indicator of Movement:
	Measured in square centimetres to indicate the spatial distribution of movement
Micro events	Indicator of Movement:
	Measured whenever participant moves more than 1 mm
Motion simplicity	Indicator of Complexity of movements:
	High scores represent small movements, low scores reflect complex movements
Omission errors	See above
Correct answers reaction time (mean)	See above
Correct answers reaction time (SD)	See above
Commission errors	See above
Normalized commission errors	Correction of commission error rate based on individual inattention levels
	Measured by the ratio of commission errors to correct responses

Description of variables were obtained from Climent et al. [25] for Nesplora Aquarium and from Qbtech for the Qb-Test.

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Darstellung des eigenen Anteils

Bei der Erstellung meiner publikationsbasierten Doktorarbeit war ich von Anfang an in die Konzeptualisierung miteingebunden und erarbeitete diese zusammen mit PD Dr. Grimm. Außerdem erarbeitete ich die Forschungsmethodik und Vorgehensweise und war an der Validierung der Ergebnisse mit Unterstützung von PD Dr. Grimm beteiligt. Ich führte die Untersuchung bei den Studienteilnehmer*innen persönlich durch. Ich war für die Rekrutierung der Studienteilnehmer*innen sowie das Bereitstellen der Materialen und Computerressourcen zuständig. Weiterhin übernahm ich die Datenerhebung. Ebenso arbeitete ich mit Unterstützung durch die wissenschaftliche Hilfskraft Behnaz Kiani an der Visualisierung. Die Durchführung und Auswertung sämtlicher statistischer Analysen erfolgten vollumfänglich durch mich, supervidiert durch PD Dr. Grimm. Ich verfasste die Arbeit vom ersten Entwurf bis hin zur endgültigen Fertigstellung inklusive der Einarbeitung der Revisionen vor und nach der Publikation. Außerdem präsentierte ich die Arbeit auf zwei Kongressen.

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Schriftliche Erklärung

Ich erkläre ehrenwörtlich, dass ich die dem Fachbereich Medizin der Johann Wolfgang Goethe-Universität Frankfurt am Main zur Promotionsprüfung eingereichte Dissertation mit dem Titel

A Within-Sample Comparison of Two Innovative Neuropsychological Tests for Assessing ADHD

am Zentrum der Psychischen Gesundheit, in der Klinik für Psychiatrie, Psychosomatik und Psychotherapie des Universitätsklinikums Frankfurt unter Betreuung und Anleitung von PD Dr. Oliver Grimm ohne sonstige Hilfe selbst durchgeführt und bei der Abfassung der Arbeit keine anderen als die in der Dissertation angeführten Hilfsmittel benutzt habe. Darüber hinaus versichere ich, nicht die Hilfe einer kommerziellen Promotionsvermittlung in Anspruch genommen zu haben.

Ich habe bisher an keiner in- oder ausländischen Universität ein Gesuch um Zulassung zur Promotion eingereicht. Die vorliegende Arbeit wurde bisher nicht als Dissertation eingereicht.

Vorliegende Ergebnisse der Arbeit wurden in folgendem Publikationsorgan veröffentlicht:

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