Ein multimodaler Ansatz zur Untersuchung von neuronalen Netzwerken und Verhalten in der Interaktion mit Essen sowie deren klinischer Implikationen

Dissertation

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1. Zusammenfassung in Deutsch und in Englisch

Psychische Erkrankungen, deren Diagnostik und effektive Behandlung, stellen eine zentrale Herausforderung für die Gesellschaft und das Gesundheitssystem dar. Gerade die Binge-Eating-Störung (BES), eine Essstörung mit wiederkehrenden Essanfällen ohne kompensatorische Maßnahmen, gewinnt aufgrund steigender Prävalenz in der Gesamtbevölkerung und häufiger Komorbidität mit somatischen Diagnosen wie Diabetes-2 und Adipositas zunehmend an Bedeutung. Zur Erweiterung des transdiagnostischen Erkenntnisstands und zur Entwicklung darauf basierender innovativer, neuer Behandlungsansätze bei der BES bieten sich vor allem multimodale Ansätze an. Multimodale Ansätze verbinden verschiedene experimentelle Ansätze und Technologien wie bildgebende Verfahren, Neuromodulation, virtuelle Realität (VR), selbstberichtete Fragebögen, semi-strukturierte klinische Interviews und experimentelle Paradigmen zur Operationalisierung kognitiver Funktionen, um dadurch ein ganzheitliches und umfassendes Gesamtbild spezifischer psychologischer Phänomene und psychopathologischer Phänotypen zu erhalten. In der vorliegenden Dissertation wurden mithilfe multimodaler Ansätze kognitive, neurobehaviorale und symptom-assoziierte Prozesse bei Konfrontation mit Nahrungsreizen in Stichproben mit und ohne BES untersucht. Gewonnene Erkenntnisse tragen dazu bei, ein tieferes Verständnis von spezifischen Symptomen der BES, aber auch von essensbezogenen Kognitionen im Allgemeinen und den zugrundeliegenden Prozessen zu erhalten. Somit kann der grundlagenforschungsorientierte Wissensstand zur Objektivierung essensbezogener Kognitionen in diesem Bereich erweitert werden; es können aber auch neue Erkenntnisse bezüglich klinischer Implikationen, einer objektiven Operationalisierung und neuer Behandlungsansätze bei der BES gewonnen werden. Im Bereich der Grundlagenforschung konnte gezeigt werden, dass differentielle Effekte bei der manuellen Interaktion mit Essen in der VR bei Personen mit und ohne BES existieren und dies die Annahme eines impulsiven und reflektierenden Systems stützt (Reflective-Impulsive Model; RIM). So fand sich eine schnelle, impulsive erste Phase, bei der Essen schneller erkannt worden ist als nicht-essensbezogene Kontrollobjekte und bei der ein nachfolgendes Annäherungsverhalten zum Essen schneller eingeleitet wurde. In einer zweiten

Phase wurde dieses Essen jedoch langsamer eingesammelt als die Kontrollobjekte, was für die Aktivierung eines reflektierenden Systems spricht. Die manuelle Interaktion mit Essen ging bei Personen ohne BES mit einer erhöhten Aktivität im rechten dorsolateralen Präfrontalkortex (dlPFC) einher, was auf die Aktivierung eines spezifischen Essensbewertungs-Netzwerks und auf eine Interkonnektivität zwischen dlPFC und dem orbitofrontalen Kortex (OFC) hinweist. Das schnellere Kategorisieren und Einleiten eines Annäherungsverhaltens bei Personen mit BES deckt sich mit der Annahme einer erhöhten essensbezogenen Impulsivität, steht jedoch im Kontrast zum Befund des verlangsamten Einsammelns des Essens. Dies könnte allerdings auch durch möglicherweise aversive motivationale Prozesse erklärt werden. Des Weiteren konnte gezeigt werden, dass differentielle Effekte in der manuellen Interaktion mit Essen in der VR besser detektiert werden können als auf einem 2D-Touchscreen. Im Bereich neuer klinischer Implikationen zu Behandlungsansätzen der BES zeichneten sich zwei Facetten ab: Zum einen zeigte sich, dass die Validierung des neu in der VR implementierten experimentellen Paradigmas zu insensitiv erschien, um differentialdiagnostisch relevante manuelle Interaktionsmuster mit Essen bei Personen mit BES zu identifizieren und Bezüge zu spezifischen Markern der Psychopathologie, des Essverhaltens, des Verlangens nach Essen oder der generellen Impulsivität herzustellen. Zum anderen zeigte sich, dass die Verbindung eines kognitiven Trainings zur Modifikation einer kognitiven Aufmerksamkeitsverzerrung gegenüber Essen bei Patienten mit BES mit nicht-invasiver Hirnstimulation einen vielversprechenden Ansatz bieten könnte. So konnte die Inhibitionsfähigkeit mithilfe von 2 mA anodaler transkranieller Gleichstromstimulation des rechten dlPFC in einem experimentellen Paradigma gesteigert werden und ein neuromodulationsunspezifischer Effekt bei der Reduktion von Binge-Eating-Episoden während der Studienteilnahme über 3 Messzeitpunkte hinweg beobachtet werden. Zusätzlich schienen vor allem Personen mit erhöhter prädisponierter neuronaler Ressourcenallokation im EEG, nämlich der P3-Komponente, von neuromodulationsgestützten Trainings profitieren zu können, was Evidenz liefert, dass insbesondere interindividuell abgestimmte kognitive Trainings zu einer maximalen Effektivität bei der Behandlung von BES führen könnte.

Psychic diseases, its diagnostic and effective treatment represent a central burden for society and the public health system. Especially the Binge-Eating-Disorder (BED), an eating disorder characterized by recurrent binge eating episodes without compensatory behaviour, comes into focus due to rising prevalence in the population and associated somatic comorbidities like Diabetes-2 and obesity. To extent transdiagnostic knowledge and, based on that, to develop effective, innovative and novel treatments for the BED, multimethod research seems to be key. Multimethod research combines experimental approaches and technologies like neuroimaging, neuromodulation, virtual reality (VR), self-report questionnaires, semi-structured clinical interviews and experimental paradigms to operationalize cognitive functions to get a holistic view on specific psychological phenomena and psychopathological phenotypes. With the help of multimethod approaches, cognitive, neurobehavioural and symptom-associated processes during confrontation with food stimuli in samples with and without BED are investigated. These findings contribute to a deeper understanding of specific symptoms and the psychopathology of the BED, but also of food-related cognitions in general and their underlying processes. Thus, knowledge concerning basic research to objectify food-specific cognitions can be extended, as well as new clinical implications, objective operationalization and new treatment approaches for the BED can be drawn. In the domain of the basic research, it could be shown, that differential effects in the manual interaction with food in the VR are observable in a sample with BED and without BED which strengthens the assumption of a dual system consisting of an impulsive and a reflective system (Reflective-Impulsive Model; RIM). In a first fast, impulsive stage, food is recognized faster than non-food-related control objects and an approach behaviour was initiated faster subsequently. In a second stage, food was collected slower than the control objects which speaks for the presence of a reflective system. In the sample without BES the manual interaction with food was associated with an elevated activity in the right dorsolateral prefrontal cortex (dlPFC), which indicates an activation of a food-specific food-valuation network and an interconnectivity between the dlPFC and the orbitofrontal cortex (OFC). The faster categorization and initiation of the approach behaviour in the sample with BED is congruent to the assumption of an elevated food-specific impulsivity. In contrast, the slower collection of food could be

explained by aversive motivational processes. Further, it could be shown, that differential effects in the manual interaction with food are more evident in the VR than on a 2D-touchscreen. In the domain of new clinical implications for the BED, two facets became evident: On the one hand, that the newly implemented experimental paradigm in the VR seems too insensitive to detect relevant manual interaction patterns with food in people with BED and their association to specific markers of psychopathology, eating behaviour, food craving or general impulsivity. On the other hand, the combination of a cognitive training to modify cognitive biases and impulsivity-related processes towards food and non-invasive brain stimulation seems promising. Inhibitory control could be enhanced by the application of 2 mA anodal transcranial direct current stimulation (tDCS) to the right dlPFC in an experimental paradigm. Further, a neuromodulatory-unspecific effect concerning a reduction of self-reported binge-eating episodes during the study participation across the three measurement times could be observed. Additionally, people with a predisposed higher allocation of neural ressources in the EEG, particular the P3-component, could benefit most of a tDCS-enhanced training. This supports the idea of an interindividual adaptable cognitive training to achieve a maximum of effectivity in the treatment of the BED.

2. Liste der Publikationen der Dissertation

2.1. Akzeptierte Publikationen

1. Max, S.M., Plewnia, C., Zipfel, S. *et al.* (2021) Combined antisaccade task and transcranial direct current stimulation to increase response inhibition in binge eating disorder. *Eur Arch Psychiatry Clin Neurosci* 271, 17–28. https://doi.org/10.1007/s00406-020-01164-5

2. Max, S.M., Schroeder, P.A., Blechert, J. *et al.* (2021) Mind the food: behavioural characteristics and imaging signatures of the specific handling of food objects. *Brain Struct Funct* 226, 1169–1183. https://doi.org/10.1007/s00429-021-02232-9

3. İnce B, Max S.M., Plewnia, C. *et al.* (2021) A pilot event-related potentials study on mechanisms underlying a tDCS-enhanced food-specific response inhibition task for patients with binge eating disorder. *Front Psychol* 12, 721672. http://doi.org/10.3389/fpsyg.2021.721672

2.2. Noch nicht eingereichte Manuskripte

4. Max, S.M., Schag, K., Giel, K.E., & Plewnia, C. (in preparation) Behavioural biases in the interaction with food objects in virtual reality and its clinical implication for the binge eating disorder.

3. Eigenanteil

Bei den Manuskripten handelt es sich entweder um Erstautorenschaften (1.,2.,4.) oder um eine geteilte Erstautorenschaft (3.). Eine genaue Auflistung des geleisteten Anteils an den einzelnen Veröffentlichungen kann den „Erklärungen zum Anteil gemeinschaftlicher Veröffentlichungen“ im Anhang entnommen werden. Bei allen Publikationen wurden die Daten ausschließlich von S. Max erhoben. Bei 2. und 4. wurde die Studie durch S. Max mit Unterstützung von C. Plewnia konzipiert. In allen Studien wurde die statistische Auswertung und deren inhaltlichen Interpretationen ausschließlich von S. Max durchgeführt mit Unterstützung des Letztautors. Die Aufbereitung der oben aufgeführten Manuskripte erfolgte durch S. Max mit Unterstützung des Letztautors.

4. Einleitung

Essen stellt aus evolutionärer Sicht unser Überleben sicher. Ohne Essen kein Leben. Auf der anderen Seite ist Essen aber auch mit gesundheitlichen Gefahren verbunden, seien es Übergewicht oder auch Essstörungen (Krebs, 2009; Södersten, Bergh, & Zandian, 2006). Gerade bei der Konfrontation mit Nahrungsreizen sind kognitive und neurobehaviorale Prozesse verändert (Hardman et al., 2021; Werthmann, Jansen, & Roefs, 2015) und diese Veränderungen scheinen eine zentrale Rolle bei der Entwicklung und Aufrechterhaltung von Essstörungen zu spielen (Williamson, Muller, Reas, & Thaw, 1999; Williamson, White, York-Crowe, & Stewart, 2004). Bereits frühe kognitive und neuropsychologische Veränderungen in der Kindheit könnten somit zur Entwicklung einer Essstörung führen (Kothari, Rosinska, Treasure, & Micali, 2014; Kothari, Solmi, Treasure, & Micali, 2013). Mit einer Lebenszeitprävalenz von bis zu vier Prozent gehört die Binge-Eating-Störung (BES) zu der am meisten vertretenen Essstörung und tritt somit häufiger auf als Anorexia Nervosa und Bulimia Nervosa (Keski-Rahkonen & Mustelin, 2016; Kessler et al., 2013; Smink, Van Hoeken, & Hoek, 2012). Die BES ist durch wiederkehrende Essanfälle gekennzeichnet, bei denen die betroffenen Personen von einem Kontrollverlust ihres Essverhaltens berichten. Innerhalb eines umschriebenen Zeitraums wird eine größere Menge an Essen konsumiert, obwohl man sich nicht körperlich hungrig fühlt. Es wird schneller als gewöhnlich und bis zu einem unangenehmen Völlegefühl gegessen. Oft findet das Essen allein statt. Die Betroffenen schämen sich, in Gegenwart anderer so viel zu essen, verspüren aber auch sich selbst gegenüber Ekel- und Schuldgefühle. Wie bei anderen psychischen Erkrankungen ist auch bei den Essstörungen der Leidensdruck ein zentrales Leitsymptom (American Psychiatric Association, 2013). Da die BES oft von Komorbiditäten wie Diabetes-2, Übergewicht und Schmerzstörungen begleitet ist, berichten Personen mit BES auch von einer geringeren Lebensqualität und vermehrten körperlichen Einschränkungen. Dies wiederum ist aufgrund zunehmender Inanspruchnahme des Gesundheitssystems mit erhöhten Kosten assoziiert (Agh et al., 2015; Vancampfort et al., 2014). Leitlinien empfehlen die Behandlung mit Verhaltenstherapie. Allerdings remittieren nur rund 50% nach einer Behandlung (Deutsche Gesellschaft für Essstörungen (DGESS), 2018). Um alternative Behandlungen anbieten zu können, bedarf es

neuer Ansätze und eines besseren Verständnisses zugrundeliegender kognitiver und neurobehavioraler Mechanismen. Gerade multimodale Ansätze, die verschiedene Technologien wie bildgebende Verfahren, Neuromodulation und virtuelle Realität (VR) verbinden, bieten sich an, um psychologische und psychopathologische Phänomene ganzheitlich betrachten und verstehen zu können (Brewer & Hunter, 1989).

Verschiedene Modelle liefern Theorien zu diesen zugrundeliegenden kognitiven Mechanismen. So werden grundlegend zwei Systeme unterschieden, die sich gegenseitig regulieren: ein impulsives und ein reflektierendes System (Reflective-Impulsive Model; RIM) (Metcalfe & Mischel, 1999; Strack & Deutsch, 2004). Während das reflektierende System Verhaltensentscheidungen aufgrund von Wissen und Werten fällt, werden Verhaltensentscheidungen vom impulsiven System durch assoziative Verbindungen und motivationale Prozesse geleitet. Diese beiden Systeme können über ein kognitives Kontrollsystem moduliert werden, wodurch ein bestimmtes Ess- und Gesundheitsverhalten gebahnt wird (Friese, Hofmann, & Wiers, 2011). Im Bereich der BES ist der Kontrollverlust über das Essverhalten sehr eng mit essensbezogener Impulsivität verknüpft (Giel, Teufel, Junne, Zipfel, & Schag, 2017). Diese Impulsivität umfasst zwei Facetten, zum einen eine erhöhte Sensitivität gegenüber belohnenden Reizen und zum anderen ein gesteigertes spontanes und unüberlegtes Verhalten bei reduzierter Inhibitionsfähigkeit (Dawe & Loxton, 2004; Gullo, Loxton, & Dawe, 2014). Eine Exekutivfunktion, um diese Impulsivität zu regulieren und geplantes Verhalten durchzuführen, ist hierbei die kognitive Kontrolle, wodurch sich eine Schnittmenge mit dem reflektierenden System innerhalb des Reflective-Impulsive Models ergibt (Braver, 2012). Kognitive Kontrolle umfasst eine komplexe Verknüpfung und Koordination von sensorischen, motorischen und kognitiven Systemen zur Erreichung eines spezifischen Ziels (Koechlin, Ody, & Kouneiher, 2003; Miller & Cohen, 2001). Das Spektrum der kognitiven Kontrolle ist hierbei weit gefächert, so wird sie bei der Selektion und Verarbeitung von Information (Ridderinkhof, Ullsperger, Crone, & Nieuwenhuis, 2004), bei der Überwachung und Lösung von Konflikten (Botvinick, Braver, Barch, Carter, & Cohen, 2001), dem Ignorieren irrelevanter Reize zur Erreichung eines zielgerichteten Verhaltens (Lavie, Hirst, De

Fockert, & Viding, 2004) und bei der Inhibition von Reflexen und habituellen Reaktionen (Miller, 2000) benötigt.

Bereits in nicht-klinischen Stichproben zeigen sich Veränderungen kognitiver und neuronaler Prozesse bei Nahrungsreizen im Vergleich zu neutralen Reizen. Um schnelle Orientierungsreaktionen und Erkennungsprozesse zu operationalisieren, wird die visuelle Dotprobe-Aufgabe verwendet. Wenn Nahrungsreize schnelle Orientierungsreaktionen hervorrufen, sollte der danach präsentierte Probe schneller erkannt werden, sofern er am selben Ort wie der Nahrungsreiz präsentiert wurde (MacLeod, Mathews, & Tata, 1986). Hier fand man, dass selbst normal-gewichtige Personen ohne Essstörungen eine schnellere Orientierungsreaktion hin zu Essensstimuli als zu Kontrollstimuli zeigten (Castellanos et al., 2009; Doolan, Breslin, Hanna, Murphy, & Gallagher, 2014; Loeber et al., 2012; McGeown & Davis, 2018; Nijs, Muris, Euser, & Franken, 2010). Im Bereich der Exekutivfunktionen spielt die inhibitorische Kontrolle eine zentrale Rolle. Inhibitorische Kontrolle umfasst die Fähigkeit, ziel-irrelevante Ziele zu ignorieren, impulsive Verhaltensweisen zu unterdrücken und zeitgleich zielgerichtetes Verhalten aufrecht zu erhalten (Tiego, Testa, Bellgrove, Pantelis, & Whittle, 2018). In der Stroop-Aufgabe müssen hierbei aufgabenirrelevante Reize ignoriert und auf spezifische Eigenschaften des Zielreizes reagiert werden. Auch hier zeigten Personen ohne Essstörungen eine verringerte Inhibitionskontrolle, wenn Nahrungsstimuli als Zielreiz fungierten (Long, Hinton, & Gillespie, 1994; Nijs, Franken, & Muris, 2010; Phelan et al., 2011). Andere experimentelle Aufgaben, in denen inhibitorische Kontrolle erforderlich ist, sind unter anderem die Stop-Signal-Aufgabe (SST) und die Go/No-Go-Aufgabe. Hier müssen ebenfalls aufgabenirrelevante, aber sehr saliente Reize ignoriert werden. Auch hier reagieren bereits Personen ohne Essstörungen auf Essensreize schneller und machen hierbei mehr Fehler (Batterink, Yokum, & Stice, 2010; Houben, Nederkoorn, & Jansen, 2014; Teslovich et al., 2014). Bei Personen mit einer klinisch bedeutsamen Essstörung wie der BES scheinen diese kognitiven Bereiche noch stärker verändert zu sein als bei vergleichbaren Kontrollgruppen. So ist die inhibitorische Kontrolle bei Personen mit BES verringert (Manasse et al., 2016; Popien, Frayn, von Ranson, & Sears, 2015; Schag et al., 2013; Svaldi, Naumann, Trentowska, & Schmitz, 2014), sowie die impulsive Orientierungsreaktion zu Nahrungsreizen hin stärker

ausgeprägt (Bongers et al., 2015; Deluchi, Costa, Friedman, Gonçalves, & Bizarro, 2017; Sperling, Baldofski, Lüthold, & Hilbert, 2017; Svaldi, Schmitz, et al., 2014). Eine Metaanalyse zeigt, dass insbesondere die Bereiche der kognitiven Flexibilität, inhibitorischer Kontrolle, Aufmerksamkeit und Planungsfähigkeit bei Personen mit BES gegenüber Kontrollgruppen schwächer ausgeprägt sind (Iceta et al., 2021). In der Forschung mit der BES wurde die Antisakkadenaufgabe als Instrument zur Operationalisierung von kognitiver Kontrolle und Impulskontrolle eingesetzt. Bei der Antisakkadenaufgabe muss eine automatische Blickbewegung auf einen neu erscheinenden Stimulus im Sichtfeld unterdrückt und umgelenkt werden (Antoniades et al., 2013; Hutton & Ettinger, 2006). In einer Antisakkadenaufgabe mit Essensstimuli konnte bereits gezeigt werden, dass Personen mit BES mehr Probleme hatten, Sakkaden auf die Essensstimuli zu inhibieren als Personen ohne BES (Schag et al., 2013). Erste Ansätze, die Antisakkadenaufgabe als Intervention zur Reduktion von Binge-Eating-Episoden einzusetzen, waren vielversprechend (Giel, Schag, Plewnia, & Zipfel, 2013).

Auf biopsychologischer Ebene spielt dabei der dorsolaterale Präfrontalkortex (dlPFC) eine zentrale Rolle. Kognitive Kontrolle und Verhaltensinhibition sind sehr eng an den dlPFC geknüpft (Cole & Schneider, 2007; Egner & Hirsch, 2005; Miller & Cohen, 2001). Vor allem bei Aufgaben, bei welchen ein spontaner Handlungsimpuls unterdrückt und ein alternatives Verhalten eingeleitet werden muss, ist der dlPFC beteiligt (Blasi et al., 2006; Figner et al., 2010; Garavan, Ross, Murphy, Roche, & Stein, 2002; Knoch & Fehr, 2007; Simmonds, Pekar, & Mostofsky, 2008). Auch im Bereich der Selbstkontrolle, wenn Personen Essverhalten regulieren, spielt der dlPFC eine zentrale Rolle (F. Chen, He, Han, Zhang, & Gao, 2018; Rösch et al., 2021). Gerade bei der BES scheint eine reduzierte Aktivität im dlPFC mit verringerter Inhibitionsfähigkeit einherzugehen (Lavagnino, Arnone, Cao, Soares, & Selvaraj, 2016; Lee, Namkoong, & Jung, 2017; Veit et al., 2021). Darüber hinaus ist bei der Verarbeitung von Information und der Integration anderer kortikaler Bereiche der dlPFC wichtig. So werden im Rahmen eines Essensbewertungs-Netzwerks hedonische Werte von Reizen im orbitofrontalen Kortex (OFC) verarbeitet und an den dlPFC gesendet, um dort ein spezifisches Verhalten einzuleiten (Camus et al., 2009; Petrides & Pandya, 1999). Insbesondere Nahrungsreize führen zu einer starken Aktivierung im OFC, sodass

von einer starken Interkonnektivität zwischen dlPFC und OFC auszugehen ist (Killgore et al., 2003; Morris & Dolan, 2001).

Um Zusammenhänge und Kausalitäten von neuronalen Aktivitäten auf Verhaltensebene zu erforschen, gibt es eine Vielzahl technologischer Möglichkeiten. Um Rückschlüsse auf Kausalität ziehen zu können, bietet sich die non-invasive Hirnstimulation an. Durch Applikation von schwachem elektrischem Gleichstrom (1-2 Milliampere (mA)) wird neuronale Erregbarkeit in kortikalen Bereichen verändert und dadurch gezielt Aktivität im zentralen Nervensystem beeinflusst (Jáuregui-Lobera & Martínez-Quiñones, 2018). Durch anodale transkranielle Gleichstromstimulation (engl. transcranial direct current stimulation = tDCS) kommt es meist zu aktivitätserhöhenden Effekten, während kathodale tDCS aktivitätshemmende Effekte zeigt (Lewis, Thomson, Rosenfeld, & Fitzgerald, 2016). Eine Meta-Analyse konnte zeigen, dass ein kleiner, aber signifikanter positiver Effekt von tDCS bezüglich der Verhaltensinhibition existiert, dies jedoch abhängig ist von der Montage der angebrachten Anode und Kathode, sowie dem stimulierten Areal (Schroeder, Schwippel, Wolz, & Svaldi, 2020). Erfolgsversprechende Behandlungsergebnisse mit tDCS konnten bei der Behandlung von Depressionen, Schlaganfällen, Schizophrenie, Schmerzstörungen, Substanzmissbrauch und Zwangsstörungen gefunden werden (George & Aston-Jones, 2010; Tracy & David, 2015). Im Bereich von BES gibt es allerdings nur wenig Befunde bezüglich der Effektivität von tDCS. Meist werden Effekte von tDCS auf essensbezogenes Verlangen in nicht-klinischen Stichproben oder Stichproben mit anderen Essstörungen untersucht (McClelland, Bozhilova, Campbell, & Schmidt, 2013). In einer Studie mit BES-Patienten konnte das Verlangen nach Essen und die tatsächliche Nahrungsaufnahme durch anodale Stimulation des rechten dlPFC reduziert werden (Burgess et al., 2016). Um Zusammenhänge zwischen neuronaler Aktivität und Verhalten zu untersuchen, gibt es eine Reihe von bildgebenden Verfahren, die mit verschiedenen Vor- und Nachteilen einhergehen. Mithilfe einer Elektroenzephalographie (EEG) können ereigniskorrelierte Potentiale (engl. event-related potentials = ERP) abgeleitet werden, die kortikale Aktivität in hoher zeitlicher Auflösung abbilden (Luck, 2014). EEG wurde bereits eingesetzt, um Verhaltensinhibition im Bereich essensbezogener kognitiver Prozesse zu untersuchen. Besonders zentral erscheinen hierbei die ERPs N2, P3 und ERN

(error-related negativity). Die N2, eine negative negative ERP-Welle, deren Amplitude den höchsten Ausschlag zwischen 200 und 300ms nach Stimuluspräsentation erreicht, steht in enger Verbindung zu inhibitorischer Kontrolle und der Kontrolle von automatischen Verhaltenstendenzen (Falkenstein, 2006). Andere Autoren hingegen argumentieren, dass eine andere Facette der kognitiven Kontrolle, nämlich die der Konfliktüberwachung, besser durch die N2 operationalisiert wird (Donkers & Van Boxtel, 2004). Die P3, eine positive ERP-Welle, deren Amplitude den höchsten Ausschlag zwischen 300 und 600ms nach Stimuluspräsentation erreicht, hingegen ist assoziiert mit weiter gefächerten Exekutivfunktionen wie Aufmerksamkeit, Gedächtnis, Motivation und Verhaltensinhibition (Dimoska, Johnstone, & Barry, 2006). Eine Metaanalyse legt nahe, dass die P3 eher kein spezifischer Marker der inhibitorischen Kontrolle ist (Huster, Messel, Thunberg, & Raud, 2020), und die P3 vielmehr Prozesse der Aufmerksamkeit, der Stimuluswahrnehmung und -verarbeitung gerade von neuen Reizen operationalisiert (Friedman, Cycowicz, & Gaeta, 2001). Bei der ERN, eine negative ERP-Welle, deren Amplitude den höchsten Ausschlag zwischen 40 und 150ms nach einer Reaktion erreicht, handelt es sich um kortikale Aktivität, die besonders ausgeprägt ist, wenn Personen Fehler bewusst detektieren, tritt aber auch bei unbewussten Fehlern auf, und ist eng verknüpft mit den Prozessen der Konfliktüberwachung (Botvinick, Cohen, & Carter, 2004; Nieuwenhuis, Ridderinkhof, Blom, Band, & Kok, 2001). Neurophysiologisch scheint der dlPFC bei der Entstehung der ERN beteiligt zu sein, wodurch ein Zusammenhang mit der kognitiven Kontrolle existieren könnte (Hester, Foxe, Molholm, Shpaner, & Garavan, 2005; Roche, Garavan, Foxe, & O'Mara, 2005). Befunde hinsichtlich dieser ERPs bei der Verhaltensinhibition und der BES variieren jedoch stark zwischen den Studien. So konnten einerseits kürzere N2 Latenzen bei Personen mit BES als bei Personen ohne BES gefunden werden und zugleich größere Amplituden der ERN bei Fehlern (Leehr et al., 2018). In einer anderen Studie konnten verringerte Amplituden der N2 und P3 bei Personen mit Übergewicht im Vergleich zu Personen ohne Übergewicht gefunden werden. Darüber hinaus hing die N2 mit klinischen Markern des Essverhaltens zusammen (Iceta et al., 2020). In einer anderen EEG-Studie konnte dieser differentielle ERP-bezogene Effekt bei Personen mit Übergewicht gegenüber Personen ohne Übergewicht nicht gefunden

werden (Biehl, Keil, Naumann, & Svaldi, 2020). Ein bildgebendes Verfahren, bei dem die zeitliche Auflösung nicht so hoch wie die des EEG ist, welches jedoch ein höheres Maß an Toleranz gegenüber Bewegungsartefakten zeigt, ist die funktionelle Nahinfrarotspektroskopie (fNIRS). Hierbei wird die Relation von oxigeniertem und deoxigeniertem Blut im Gehirn als Indikator für Hirnaktivität herangezogen (Fallgatter, Ehlis, Wagener, Michel, & Herrmann, 2004). Im Bereich von Essverhalten und essensbezogenen Kognitionen ist der Einsatz von fNIRS nur wenig erforscht. In einer Studie von Rösch et al. (2021) zeigte sich bei Personen mit BES gegenüber Personen ohne BES eine Hypoaktivierung des dlPFC im fNIRS. Dass diese Hypoaktivierung des dlPFC bei erforderlicher Verhaltensinhibition jedoch reversibel ist, zeigte eine Psychotherapiestudie von Veit et al. (2021): Die Personen mit BES, die sich in der aktiven Behandlungsgruppe befanden, zeigten eine erhöhte Aktivität des rechten dlPFC im fNIRS in einer Go/No-Go-Aufgabe im Vergleich zum Behandlungsbeginn. Bezüglich Kontrollverlust bei Essen zeigten sich auch unterschiedliche Aktivierungsmuster im fNIRS. So war der Kontrollverlust bei Aktivierung des medialen Präfrontalkortex stärker ausgeprägt als bei Aktivierung des linken Präfrontalkortex (lPFC) (Thomopoulos et al., 2019). Eine vierte Studie mit fNIRS fand, dass bevorzugte Nahrungsmittel im Vergleich zu Nahrungsmitteln, die als weniger positiv wahrgenommen wurden, zu einer verringerten regionalen Hirnaktivität im anterioren Präfrontalkortex (aPFC) führten (Minematsu, Ueji, & Yamamoto, 2018).

Um komplexe kognitive Prozesse und deren zugrundliegende neuronale Korrelate in einer kontrollierten, aber dennoch naturalistischen Umgebung mit vielen individuell einstellbaren Freiheitgraden zu untersuchen, bietet sich die virtuelle Realität (VR) an. Gerade in Kombination mit Sensoren zum Tracking von Bewegungen können dadurch komplexe Interaktionsmuster mit Nahrungsmitteln untersucht werden. In diesem Zusammenhang soll die *Embodiment*-Theorie eingeführt werden. Hierbei wird angenommen, dass der Körper der agierenden Person einen zentralen Einfluss auf die Modulation von kognitiven Prozessen hat und dass körperbezogene kognitive Prozesse stärker abgebildet werden, wenn der eigene Körper auch im Sinne von Körperbewegungen mit einbezogen wird (Shapiro, 2019). So konnte bereits gezeigt werden, dass in einer Aufgabe, bei der je nach Hinweisreiz Essen oder Bälle eingesammelt oder weggeschlagen werden

sollten, Nahrungsstimuli in der VR schneller eingesammelt wurden als Ballstimuli (Schroeder, Lohmann, Butz, & Plewnia, 2016). Dieses Interaktionsmuster mit Nahrungsstimuli scheint in der VR für hochkalorische Nahrungsmittel stärker ausgeprägt zu sein als für niedrig-kalorische Nahrungsmittel oder Kontrollstimuli (Schroeder, Collantoni, Lohmann, Butz, & Plewnia, 2021). Auch für den tatsächlichen Konsum von Essen, bzw. für das Einkaufsverhalten von Nahrungsmitteln scheint die VR vielversprechende Ansätze zu bieten (Siegrist et al., 2019; Xu, Siegrist, & Hartmann, 2021). Im Bereich der Essstörungen wird die VR vor allem bei der Expositionstherapie und als Ergänzung in der kognitiven Verhaltenstherapie eingesetzt. Hier zeigte sich, dass der Einsatz von VR bei Übergewicht und Essstörungen eine sinnvolle Ergänzung zu kognitiver Verhaltenstherapie darstellt und der kognitiven Verhaltenstherapie als Monotherapie überlegen ist (Cesa et al., 2013; Manzoni et al., 2016; Marco, Perpiñá, & Botella, 2013; Perpiñá et al., 1999; Riva et al., 2006; Riva, Bacchetta, Cesa, Conti, & Molinari, 2003, 2004). Auch bei der Behandlung einer Körperbildverzerrung scheint die VR einer in-vivo-Exposition ebenbürtig zu sein (Ferrer-García & Gutiérrez-Maldonado, 2012). Für den Einsatz von VR in der Grundlagenforschung zur Untersuchung essensbezogener Kognitionen bei der BES gibt es aber zum jetzigen Stand wenige Befunde.

Erkenntnisse, die aus der Grundlagenforschung mit gesunden Probanden und Probanden mit Essstörungen wie der BES gewonnen werden, können dazu genutzt werden, um neue Wege sowohl für die Diagnostik als auch zur effektiveren Behandlung von Essstörungen aufzuzeigen. Ein bereits sehr lange vertretener Ansatz des Reduktionismus (Oppenheim & Putnam, 1958) stellt hierbei einen Ansatz dar, der über die Zeit hinweg immer weiter modifiziert und angepasst wurde. Zentrale Annahme hierbei ist, dass ein psychologisches Phänomen mit einem physikalischen Phänomen verknüpft ist, also eine reziproke Wechselwirkung zwischen Ursache und Phänomen besteht. In neueren Theorien wird nun davon ausgegangen, dass bestimmte Facetten und Symptome einer psychischen Erkrankung nicht nur Folge der Erkrankung sind, sondern eine zentrale Rolle bei der Entwicklung und Aufrechterhaltung der psychischen Erkrankung spielen (Barendregt & van Rappard, 2004; Kievit et al., 2011). Diese Theorie wurde ständig erweitert, sodass neue Modelle nicht nur einzelne Facetten sondern ein Netzwerk

aus Facetten und phänotypischen Symptomen erfassen, die zur Entstehung und Aufrechterhaltung der Erkrankung beitragen (Borsboom & Cramer, 2013; Cramer, Waldorp, Van Der Maas, & Borsboom, 2010). Im Umkehrschluss impliziert dies, dass durch die Modifikation von Facetten und phänotypischen Symptomen eine Veränderung auf der übergeordneten Ebene der psychischen Erkrankung einhergeht. So kann durch Veränderungen auf der Ebene der Kognition und Neuroplastizität eine Verbesserung auf der übergeordneten Ebene der psychischen Erkrankung evoziert werden (Keshavan, Vinogradov, Rumsey, Sherrill, & Wagner, 2014). Erste Befunde zeigen sich diesbezüglich auch bereits im Bereich der BES. So lassen sich Zusammenhänge zwischen kognitiven Verzerrungen und der psychopathologischen Ebene bei der BES finden. Eine größere kognitive Verzerrung bei Nahrungsreizen, ergo eine schlechtere Performanz in einer experimentellen Aufgabe, geht mit einer stärker ausgeprägten Krankheitssymptomatik einher. So war ein Zusammenhang zwischen früherer und schnellerer visueller Verarbeitung von Nahrungsreizen mit einem höheren Schweregrad der BES gegeben (Iceta et al., 2020; Schmitz, Naumann, Trentowska, & Svaldi, 2014). Diese Befunde werden im Sinne reduktionistischer Ansätze genutzt, um die Effektivität kognitiver Trainings zur Behandlung der BES zu untersuchen. Dabei besteht die Annahme, dass durch eine Verringerung kognitiver Verzerrungen und auch der damit verbundenen neuroplastischen Veränderungen gegenüber Nahrungsreizen, eine Verbesserung der klinisch relevanten Symptomatik erfolgt. Erste randomisierte Trainingsstudien unterstützen diese enge Interkonnektivität zwischen Kognition und Psychopathologie und konnten zeigen, dass eine Verringerung der kognitiven Verzerrungen eine Reduktion in der psychopathologischen Symptomatik zur Folge hatte (Brockmeyer et al., 2019; Schmitz & Svaldi, 2017). Grundlegende Idee dieser kognitiven Trainings ist die Annahme, dass zwischen spezifischen Symptomen einer psychischen Erkrankung und kognitiven oder psychophysiologischen Veränderungen ein kausaler Zusammenhang im reduktionistischen Sinne besteht (Putnam, 1973). Diese kognitiven oder psychophysiologischen Veränderungen können bei Personen ohne diese spezifischen Symptome nicht gefunden werden, was eine Krankheitsspezifität nahelegt (Iceta et al., 2021). Diese impliziert, dass eine Anpassung der veränderten kognitiven oder psychophysiologischen

Ressourcen bei Personen mit spezifischen psychologischen Erkrankungen an das Level der kognitiven und psychophysiologischen Ressourcen von Personen ohne ebenjene psychologischen Erkrankungen zu einer Remission führen sollte. Um solche kognitive Trainings zu konzipieren, bedarf es jedoch zunächst grundlagenorientierter Forschung, die experimentelle Paradigmen an Probanden mit und ohne Essstörungen validiert und weiterentwickelt, um eine möglichst hohe ökologische und symptomatologische Validität zu erreichen. Multimethodische Ansätze, die zugrundeliegende kognitive, neuronale und behaviorale Prozesse gleichzeitig untersuchen, erscheinen hierbei am vielversprechendsten.

5. Zielsetzung

Die vorliegende Arbeit verfolgt das Ziel, mithilfe eines multimodalen Ansatzes und der Kombination etablierter und neuartiger Technologien den wissenschaftlichen Erkenntnisstand bezüglich kognitiver Verzerrungen bei Nahrungsstimuli und deren neurophysiologischer Korrelate in klinischen und non-klinischen Stichproben zu validieren und zu erweitern. Resultierende klinische Implikationen für die BES werden abschließend kritisch beleuchtet.

Das Dissertationsprojekt besteht aus zwei Teilen: Die gewonnenen Erkenntnisse aus den Publikationen Max, Schroeder, et al. (2021), Max, Plewnia, et al. (2021) und İnce, Max, et al. (2021) sollen in die Publikation Max, Schag, et al. (in preparation) einfließen. In Max, Schroeder, et al. (2021) wird zunächst durch multimodale Diagnostik ein neues experimentelles Paradigma validiert. In einer VR sollen Probanden ohne Essstörungen in einem Two-Choice-Forced-Choice-Paradigma mit Essensobjekten durch tatsächliche Handbewegungen über Nah-Infrarot-Tracking (Leap Motion) interagieren. Parallel dazu wird regionale Hirnaktivität über fNIRS gemessen. In Max, Plewnia, et al. (2021) und İnce et al. (2021) werden in einer klinischen Stichprobe mit diagnostizierter BES an einem bereits etablierten experimentellen Paradigma neurobehaviorale Phänomene untersucht. Die Probanden führen eine Antisakkadenaufgabe mit Essensstimuli am Eye-Tracker (ET) durch. Der Einfluss von Neuromodulation in Form von anodaler tDCS und psychophysiologischen Maße im EEG auf die Performanz in der Antisakkadenaufgabe und deren klinische Bedeutsamkeit soll hierbei exploriert werden. Abschließend soll in Max, Schag, et al. (in preparation) das neu etablierte experimentelle Paradigma von Max, Schroeder, et al. (2021) in einer klinischen Stichprobe mit diagnostizierter BES in einem prä-post-Design untersucht werden. Differenzialdiagnostische Effekte der Psychopathologie bei der BES auf die Interaktion mit Essensobjekten in der VR und deren klinische Implikationen werden hierbei exploriert.

6. Ergebnisse und Diskussion

In einer ersten Studie mit Probanden ohne Essstörungen sollte zunächst ein neues experimentelles Paradigma untersucht und validiert werden (Max, Schroeder, et al., 2021). In der VR sollten die Probanden je nach Blockinstruktion entweder das Essen, den Ball oder den Bürogegenstand einsammeln. Ziel- und Distraktorstimulus wurden gleichzeitig nebeneinander präsentiert. Dadurch sollte eine Situation evoziert werden, bei der kognitive Kontrolle nötig ist, da aufgabenirrelevante Information, in diesem Fall ein Distraktorstimulus, ausgeblendet werden musste. Es sollte nur auf den Zielstimulus reagiert werden und ein entsprechendes zielgerichtetes Annäherungsverhalten eingeleitet werden. Die Bälle und die Bürogegenstände fungierten hierbei als Kontrollstimuli für das Essen, wobei die Bälle als Marker der individuellen motorischen Grundgeschwindigkeit verwendet wurden. Auf der Verhaltensebene wurden Aufmerksamkeitsprozesse und manuelle Interaktionsprozesse untersucht. Operationalisiert wurden diese beiden Prozesse durch zwei Marker: Den ersten Marker bildete der Zeitpunkt, zu dem die Versuchsperson eine standardisierte Startposition mit der Hand verließ, um den entsprechenden Zielstimulus einzusammeln. Der Zielstimulus wurde also korrekt erkannt und kategorisiert. Den zweiten Marker bildete die Zeitdauer, die die Versuchsperson benötigte, um nach dem Verlassen der Startposition den Zielstimulus einzusammeln. Parallel zu der Aufgabe wurde regionale Hirnaktivität über fNIRS gemessen. Darüber hinaus wurde das experimentelle Paradigma auf einem 2D-Touchscreen repliziert. Durch differentielle Effekte von VR gegenüber Touchscreen sollten neue Erkenntnisse bezüglich der Wahl des optimalen Mediums zur Modellierung von nahrungsbezogenen Kognitionen gewonnen werden. In der Studie konnten solche differentiellen Effekte bei der Interaktion mit Nahrungsstimuli gefunden werden. Insgesamt konnte beobachtet werden, dass die Interaktion mit Nahrungsmitteln mit erhöhter neuronaler Aktivität im rechten dlPFC einherging. Auf der Verhaltensebene konnte auf beiden technologischen Medien (VR und Touchscreen) eine schnellere Initiierung eines Annäherungsverhaltens zu Nahrungsstimuli hin im Vergleich zu Bürogegenständen beobachtet werden. Dies deckt sich mit Befunden aus den Dot-Probe-Aufgaben, die auch schneller initiierte Aufmerksamkeitsprozesse bei Nahrungsstimuli gegenüber Kontrollstimuli zeigen

konnten (Castellanos et al., 2009; Doolan et al., 2014; Hou et al., 2011; Loeber et al., 2012; McGeown & Davis, 2018; Nijs, Muris, et al., 2010; Werthmann et al., 2013). Auf einer psychophysiologischen Ebene und unter Berücksichtigung verschiedener neurokognitiver Modelle lässt sich die schnellere Initiierung bei Nahrungsstimuli mit dem Essensbewertungs-Netzwerk erklären (Camus et al., 2009). Hierbei wird von einer Interkonnektivität von dlPFC und orbitofrontalem Kortex (OFC) ausgegangen (Petrides & Pandya, 1999). Hedonische Werte von Stimuli werden im OFC verarbeitet, an den dlPFC weitergegeben, dort verarbeitet und ein entsprechendes Zielverhalten ausgeführt. Bereits Nahrungsreize alleine lösen eine starke Reaktion im OFC aus (Killgore et al., 2003; Morris & Dolan, 2001). Nachfolgend wird entsprechend schneller ein Zielverhalten, in diesem Fall ein Annäherungsverhalten zum Nahrungsreiz hin, gebahnt. Darüber hinaus wird die Geschwindigkeit des Annäherungsverhaltens über spezifische Stimulusvalenzen moduliert. So war die Reaktionszeit schneller, wenn die Differenz der subjektiven Valenz zwischen Ziel- und Distraktorreiz größer war. Wurde ein Zielstimulus explizit deutlich positiver bewertet als der zeitgleich präsentierte Distraktorstimulus, wurde ein Annäherungsverhalten zum Zielstimulus umso schneller eingeleitet. Die erhöhte neuronale Aktivität vor allem im rechten dlPFC kann ebenfalls mit dem Essensbewertungs-Netzwerk erklärt werden. In jedem Durchgang musste der Zielreiz neu entdeckt und kategorisiert werden, sodass neuronale Ressourcen aufgewandt werden mussten, um Stimulus-spezifische Valenzen einzuschätzen und entsprechendes Zielverhalten auszuführen. Dadurch kann von einem essensspezifischen Zusatzaufwand zur Rekrutierung neuronaler Ressourcen ausgegangen werden. Auf korrelativer Ebene fand sich, dass eine erhöhte neuronale Aktivität im rechten dlPFC mit schnellerer Initiierung des Annäherungsverhalten einherging. Dies unterstützt zunächst stärker die Annahme, dass in diesem speziellen Paradigma der rechte dlPFC vorrangig daran beteiligt ist, zielgerichtetes Verhalten in der manuellen Interaktion auszuführen (Cornier, Salzberg, Endly, Bessesen, & Tregellas, 2010; Horstmann et al., 2011) und weniger daran, impulsives Verhalten zu inhibieren (Blasi et al., 2006; Mostofsky & Simmonds, 2008). In der zweiten Phase der manuellen Interaktion mit Nahrungsstimuli konnte beobachtet werden, dass Essen langsamer eingesammelt wurde als Bürogegenstände. Dies war nur in der VR und nicht auf dem

Touchscreen zu beobachten. Dies ist ein Indiz dafür, dass währenddessen ein Netzwerk kognitiver Kontrolle aktiviert ist. Da die Versuchspersonen in dieser Aufgabe explizit den Ziel- und Distraktorreiz erkennen, unterscheiden und darauf reagieren mussten, kam es möglicherweise zu einer bewussteren und möglicherweise auch vorsichtigeren Interaktion mit dem Nahrungsreiz, was ein Resultat des höheren hedonischen Werts gewesen sein könnte. Dieser Befund deckt sich nicht unmittelbar mit Befunden aus vorherigen Studien, Erklärungsansätze bietet jedoch vor allem das Design des Paradigmas. In dieser Studie sollten die Stimuli explizit erkannt und kategorisiert werden, während beispielsweise in der Studie von Schroeder et al. (2016) auf einen Zielreiz-unabhängigen Hinweisreiz (Farbe einer geometrischen Form) reagiert werden musste und entsprechend gar nicht das Zielobjekt explizit evaluiert werden musste. Da es auch keine korrelativen Zusammenhänge zwischen Verhaltensebene und neuronaler Ebene in dieser Studie gab, ist davon auszugehen, dass das Netzwerk kognitiver Kontrolle in diesem experimentellen Paradigma keine zentrale Rolle spielte und vorrangig das Essensbewertungs-Netzwerk die kognitive und neuronale Verarbeitung der Nahrungsreize modulierte. Dass die langsamere und möglicherweise kontrollierte Interaktion mit Nahrungsmitteln nur in der VR und nicht auf dem Touchscreen zu beobachten war, unterstreicht die Wichtigkeit bei der Wahl des technologischen Mediums zur Modellierung von essensbezogenen Kognitionen und deren Verarbeitungsprozesse. Gerade der größere Anteil körpergebundener Kognitionen in der VR könnte dazu geführt haben, dass ein verhaltensspezifischer Effekt in der Interaktion mit Essen nur in der VR, nicht jedoch auf dem Touchscreen zu erkennen war. Komplexeres und naturalistischeres Verhalten kann in der Interaktion mit Essen abgebildet werden, wodurch eine vorsichtigere Interaktion mit Nahrungsmitteln ein Resultat der höheren persönlichen Wichtigkeit des Objekts sein könnte. Zusammenfassend gilt, dass in dieser Studie differentielle Effekte bei der manuellen Interaktion mit Essen gefunden werden konnten, die teilweise in Verbindung zu erhöhter neuronaler Aktivität im rechten dlPFC standen. Das neue Paradigma scheint also geeignet zu sein, essensspezifische Kognitionen und zugrundeliegende neuronale Prozesse abzubilden. Auf der einen Seite wurde Essen schneller erkannt und kategorisiert als Bürogegenstände, und auf der anderen Seite wurde Essen langsamer

eingesammelt, was jedoch durch das Zusammenspiel eines Essensbewertungs-Netzwerks und eines Netzwerks kognitiver Kontrolle erklärt werden kann. Dass diese Effekte in der VR deutlicher waren als auf dem Touchscreen, verdeutlicht wie wichtig die Wahl des Mediums ist. Da es sich zunächst um eine Studie an gesunden Versuchspersonen handelte, gilt es, die diagnostische Validität des neuen experimentellen Paradigmas in einer klinischen Stichprobe mit Essstörungen, wie beispielsweise der BES, zu untersuchen.

In einer zweiten und dritten Studie sollte nun an einer klinischen Stichprobe mit diagnostizierter BES und einem etablierten experimentellen Paradigma untersucht werden, inwieweit kognitive Kontrolle durch tDCS modulierbar ist und wie Befunde auf Verhaltensebene und im EEG eine Grundlage für mögliche klinische Implikationen zur Transdiagnostik und Behandlung von BES bieten (İnce et al., 2021; Max, Plewnia, Zipfel, Giel, & Schag, 2021). Im Sinne der reduktionistischen Netzwerk-Ansätze sollten Marker auf der Verhaltens- und Psychophysiologieebene erfasst und in Bezug auf die Psychopathologie untersucht werden. Dafür wurde eine Studie im cross-over-Design konzipiert. Insgesamt gab es drei Messzeitpunkte. An Messzeitpunkt 1 (T0) wurde eine klinische essstörungspezifische Diagnostik durchgeführt, sowie Fragebögen zur Charakterisierung von Impulsivität und Essverhalten vorgelegt. Zusätzlich absolvierten die Probanden eine experimentelle Messung mit einer essensspezifischen Antisakkadenaufgabe mit paralleler EEG-Aufzeichnung. Zu Messzeitpunkt 2 (T1) und Messzeitpunkt 3 (T2) wurde die Antisakkadenaufgabe erneut durchgeführt, diesmal jedoch mit tDCS. Da systematisch der Effekt der applizierten Intensität von anodaler tDCS am rechten dlPFC untersucht werden sollte, wurde die Stichprobe in 2 Gruppen unterteilt. Eine Gruppe erhielt 1 Milliampere (mA), die andere erhielt 2 mA anodale tDCS. Durch die beiden tDCS-Parameter (1mA vs. 2mA) sollte eine Maximierung an effektiver Behandlung in nachfolgenden Studien im Sinne einer Dosis-Wirkungs-Beziehung gewährleistet werden. Durch das cross-over-Design erhielt jeder Proband sowohl placebo- und verum-Stimulation, entweder an T1 oder T2. Über die Probanden hinweg war die Reihenfolge von placebo- und verum-Stimulation ausbalanciert. Bei der Antisakkadenaufgabe handelt es sich um eine Aufgabe zur Operationalisierung von Impulsivität und Verhaltensinhibition, da ein sehr dominanter automatischer Reflex

auf einen neu erscheinenden Reiz im Sichtfeld unterdrückt und ein entsprechend korrigierendes Verhalten eingeleitet werden muss. Neben der Fehlerrate lassen auch Latenzen korrekter Antisakkaden Rückschlüsse auf die Inhibitionsfähigkeit zu, und zwar derart, dass eine schneller ausgeführte Antisakkade Hinweise für eine bessere Inhibitionsfähigkeit liefert (Antoniades et al., 2013). Gerade im Bereich der Forschung mit der BES zeigte sich in vorherigen Studien, dass die Antisakkadenaufgabe ein gut operationalisiertes Paradigma zur Erfassung von Impulsivität ist, bei der sich Unterschiede auf der Verhaltensebene auf der Symptomebene widerspiegeln. So zeigten Personen mit BES mehr Probleme beim Inhibieren von Sakkaden zu Nahrungsreizen als Personen ohne BES. Die Diagnose einer BES scheint also ein zentrales differentialdiagnostisches Kriterium zu sein, die die unterschiedliche Performanz in der Verhaltensaufgabe erklären könnte (Schag et al., 2013). Zunächst sollte untersucht werden, ob sich die ERPs in T0 beim Ausführen der Aufgabe unterscheiden. Hierbei waren vor allem die Amplituden der N2, ERN und P3 von Interesse. Darüber hinaus sollte untersucht werden, ob diese ERPs einen prädiktiven Wert für die Performanz bei T1 oder T2 haben und ob die ERPs mit der Psychopathologie der BES und Impulsivität zusammenhängen. Signifikante Unterschiede bezüglich der Amplituden für falsche und richtige Antisakkaden konnten gefunden werden. So war die N2-Amplitude in falschen Antisakkaden (also Fehlern) weniger ausgeprägt als bei richtigen Antisakkaden, während bei der ERN und der P3 die Amplituden bei falschen Antisakkaden stärker ausgeprägt waren als bei richtigen Antisakkaden. Dass die N2 bei falschen Antisakkaden weniger stark ausgeprägt war als bei korrekten Antisakkaden, deckt sich mit der Literatur, da eine verringerte kognitive Kontrolle und Verhaltensinhibition mit einer verringerten N2-Amplitude assoziiert ist (S. Chen, Jia, & Woltering, 2018). Auch die stärker ausgeprägte Amplitude der ERN bei falschen Antisakkaden gegenüber richtigen Antisakkaden deckt sich mit Befunden aus anderen Studien (Leehr et al., 2018). So sind Fehler mit negativer Amplitude der ERN assoziiert und korrekte Antisakkaden mit positiver Amplitude der ERN. Gerade, da sich nach dem Zeitfenster der ERN kein Unterschied mehr bezüglich der Amplituden bei falschen und richtigen Antisakkaden zeigt, könnte dies ein Hinweis für korrigierendes Verhalten sein. Neuronale Ressourcen könnten aufgewandt werden, um das ursprünglich falsche Verhalten zu korrigieren und den

Blick vom Essensstimulus abzuwenden. Dies könnte mit der *error positivity* (Pe) erklärt werden, die für Fehlererkennung und korrigierendes Verhalten verantwortlich ist (Falkenstein, Hoormann, Christ, & Hohnsbein, 2000; Nieuwenhuis et al., 2001). Bezüglich der P3 fand sich jedoch eine stärker ausgeprägt Amplitude bei falschen als bei richtigen Antisakkaden. Erklärbar ist dies durch die P3b-Komponente, die vorrangig bei Aufmerksamkeitsprozessen gegenüber salienten Stimuli aktiv ist (Nijs, Franken, & Muris, 2008). So wird in diesem Fall weniger kognitive Kontrolle durch die P3 abgebildet, sondern vielmehr neuronale Ressourcen zur Verarbeitung von Essensstimuli bei fehlerhaften Antisakkaden, da bei diesen die Essensstimuli explizit betrachtet und verarbeitet wurden. Gerade der belohnende Charakter von Essen und die damit verbundenen Schwierigkeiten, die Aufmerksamkeit davon wegzulenken, könnte diesen Effekt erklären (Biehl et al., 2020; Chami et al., 2020). Bezüglich des prädiktiven Werts der ERPs auf die Performanz in der Antisakkadenaufgabe konnten keine Zusammenhänge der N2 oder der ERN mit der Verhaltensebene gefunden werden, was sich mit Befunden essensspezifischer Inhibitionstrainings auf die N2-Amplitude deckt (Carbine et al., 2021). Gefunden werden konnten jedoch Zusammenhänge der P3-Amplitude mit der Fehlerrate an T0, T1, T2 und unter den verschiedenen Stimulationsbedingungen (Placebo- oder Verum-Stimulation). Je höher die P3-Amplitude an T0 war, desto niedriger war die Fehlerrate zu den nachfolgenden Messzeitpunkten. Da dieser prädiktive Wert der P3-Amplituden für Fehlerraten auf personenindividueller Ebene analysiert worden ist, könnte das implizieren, dass gerade die Personen, die an T0 schon in der Lage sind, neuronale Ressourcen abzurufen, stärker von einem kognitiven Training zur Verhaltensinhibition profitieren könnten (Lapenta, Di Sierve, de Macedo, Fregni, & Boggio, 2014). Da jedoch die P3-Amplitude sowohl die Leistung unter placebo- und verum-Stimulation vorhergesagt hat, ist nicht klar, ob neuromodulatorische Prozesse des tDCS in Verbindung mit der Vorhersagekraft des ERP stattgefunden haben. Zuletzt zeigten sich allerdings keine Zusammenhänge zwischen den ERPs und den klinischen Markern der BES, was sich jedoch auch mit vorherigen Befunden deckt (Iceta et al., 2020; Schaefer & Nooner, 2018). Eine signifikante negative Korrelation zeigte sich zwischen der N2-Amplitude bei korrekten Antisakkaden und nicht-planendem Verhalten, einer Subfacette von Impulsivität. Bezüglich der P3-Amplitude bei

falschen Antisakkaden fand sich ein Zusammenhang mit gezügeltem oder enthemmtem Essverhalten, was sich mit Befunden aus anderen Studien deckt (Schag et al., 2021). Eine höhere P3-Amplitude ging somit einher mit verringerter kognitiver Kontrolle und damit mit höherer Impulsivität gegenüber Nahrungsmitteln. Überraschenderweise war die P3 ebenso assoziiert mit geringerer Enthemmung, also geringerer essensbezogener Impulsivität. Diese Inkonsistenzen könnten durch die allgemein erhöhten Impulsivitätswerte in der Stichprobe erklärt werden, sodass die Probanden, die relativ gesehen weniger enthemmt erschienen, dennoch eine höhere P3-Aktivität bei fehlerhaften Antisakkaden zeigten. Grundsätzlich zeigen diese Befunde, dass Facetten von experimentellen Paradigmen teilweise wenig Konstruktvalidität hinsichtlich der Facetten von selbstberichteter Impulsivität aufweisen (Sharma, Markon, & Clark, 2014) und ERPs demzufolge eine bessere Operationalisierung von inhibitorischer Kontrolle bei Essen sein könnten (Carbine et al., 2017). Nichtsdestotrotz scheint die P3 am ehesten als Prädiktor für inhibitorische Kontrolle geeignet zu sein, wenn auch die Rolle als klinischer Marker für essensbezogene inhibitorische Kontrollprozesse detaillierter beleuchtet und erforscht werden muss.

Auf der Verhaltensebene zeigten sich sowohl non-lineare neuromodulatorische Effekte durch die tDCS als auch Lerneffekte zu den Messzeitpunkten T1 und T2. So konnte gefunden werden, dass die Gruppe, die 2 mA tDCS erhielt, unter verum-Stimulation signifikant schnellere korrekte Antisakkaden ausführte als unter placebo-Stimulation, während in der Gruppe, die 1 mA tDCS erhielt, unter verum-Stimulation signifikant schnellere korrekte Antisakkaden ausgeführt worden sind als unter placebo-Stimulation. Bezüglich der Fehlerraten gab es jedoch keine stimulationsspezifischen Effekte. Dass unter 2 mA korrekte Antisakkaden schneller ausgeführt worden sind, spricht dafür, dass insgesamt weniger kognitive Ressourcen nötig waren, um die Aufgabe durchzuführen, d.h. die Rekrutierung kognitiver Kontrolle wurde durch die anodale tDCS vereinfacht und unterstützt. Dass eine höhere Intensität der tDCS von besserer Performanz begleitet ist, konnte auch in vorherigen Studien in anderen Bereichen kognitiver Funktionen gezeigt werden (Chew, Ho, & Loo, 2015; Jamil et al., 2017). Dass gerade die Intensität von 2 mA positive Effekte hervorrief, deckt sich mit anderen positiven Befunden aus dem Bereich der Forschung mit der BES,

die ebenfalls 2 mA verwendeten (Burgess et al., 2016). Durch die Applikation von 2 mA anodaler tDCS am rechten dlPFC könnte möglicherweise die prädisponierte Hypoaktivität im rechten dlPFC bei Personen mit BES kompensiert werden, was Hinweise darauf liefert, dass die kortikale Hypoaktivität des rechten dlPFC in enger Interkonnektivität mit der Symptomebene der BES steht. In einer Aufgabe, die viel kognitive Kontrolle und Inhibitionsfähigkeit erfordert, konnte durch erhöhte neuronale Erregbarkeit entsprechender kortikaler Netzwerke die Fähigkeit zur Verhaltensinhibition gesteigert werden. Dies unterstreicht erneut die zentrale Rolle des dlPFC bei der Rekrutierung kognitiver Kontrolle und zeigt einen kausalen Zusammenhang zwischen kortikaler Erregbarkeit des rechten dlPFC und erhöhter kognitiver Kontrolle auf. Neben den non-linearen neuromodulatorischen Effekten der tDCS konnten starke Trainings- oder Lerneffekte beobachtet werden. Sowohl die Fehlerrate als auch die Geschwindigkeit korrekter Antisakkaden nahm über alle Messzeitpunkte ab, was somit eine verbesserte kognitive Kontrolle und Inhibitionsfähigkeit impliziert. Diese Verbesserung der kognitiven Kontrolle stützt die Annahme, dass kognitive Veränderungen bei Personen mit BES reversibel und modifizierbar sind und dass das gezielte Anwenden von Trainings kognitiver Kontrolle möglicherweise zur Modifikation kognitiver Verzerrungen und zur Verbesserung der Symptomebene bei der BES geeignet ist. Korrelativ fanden sich vor allem Zusammenhänge zwischen Maßen genereller Impulsivität und Maßen der Inhibitionsfähigkeit in der Antisakkadenaufgabe, jedoch keine Zusammenhänge zwischen Verhaltensebene und essensbezogener Impulsivität oder Psychopathologie der BES. Dies unterstützt erneut die Annahme, dass die verringerte Inhibitionsfähigkeit bei Personen mit BES mehr ein Problem übergeordneter Inhibitionsfähigkeit als essensbezogener Inhibitionsfähigkeit darstellt (Manasse et al., 2016). Bezüglich der klinischen Implikation eines kognitiven Trainings unterstützt durch tDCS zeigte sich ein interessanter Befund bezüglich der selbstberichteten Anzahl von Essanfällen in den letzten 7 Tagen. So gab es in der Gruppe, die 2 mA tDCS erhielt, eine signifikante Reduktion von Essanfällen, während diese Reduktion in der Gruppe, die 1 mA erhielt, nicht beobachtbar war. Die stärkste Reduktion bezüglich der Essanfälle fand jedoch von T0 auf T1 statt, d.h. tDCS wurde zu diesem Zeitpunkt noch nicht appliziert und dementsprechend kann diese Reduktion nicht durch neuromodulatorische

Prozesse erklärt werden. Dennoch fand möglicherweise ein Alltagstransfer der erforderlichen Inhibitionsfähigkeit bei der Antisakkadenaufgabe in die Psychopathologie der Probanden mit BES statt. Dies stützt erneut die Annahme, dass eine Veränderung auf der phänotypischen Verhaltensebene in direktem Zusammenhang zu Veränderungen auf der Symptomebene steht. Dass ein solcher Transfer von Labor in den Alltag stattfinden kann, konnte bereits in anderen Studien gezeigt werden (Giel, Speer, Schag, Leehr, & Zipfel, 2017; Shafran, Lee, Cooper, Palmer, & Fairburn, 2008). Eine Verbindung zwischen den neurokognitiven Einschränkungen bei der BES und der Psychopathologie kann somit vermutet werden.

Zusammenfassend lässt sich sagen, dass diese Studie verschiedene Facetten bezüglich kognitiver Prozesse und der zugrundeliegenden neuronalen Mechanismen und der damit verbundenen klinischen Implikationen aufzeigen konnte. Zum einen konnte gezeigt werden, inwieweit neuronale Prozesse im EEG prädiktiven Wert auf Verhaltensebene zu nachfolgenden Messzeitpunkten haben können. Tieferes Verständnis dieser zugrundeliegenden neuronalen Mechanismen könnte uns erlauben, bessere Schlüsse daraus zu ziehen, welche Personengruppe mit bestimmten psychophysiologischen Aktivitätsmustern von spezifischen kognitiven Trainings zur Inhibitionskontrolle profitieren könnte. Kognitive Trainings könnten dadurch spezifisch interindividuell angepasst und die Effektivität der Behandlung der BES für Subgruppen maximiert werden. Zum anderen konnte gezeigt werden, dass die verringerte Inhibitionsfähigkeit bei Personen mit BES modifizierbar ist. Zum einen konnte die verringerte kognitive Kontrolle bei Nahrungsstimuli durch Training, das heißt durch wiederholtes Ausüben einer Aufgabe, aber auch durch 2 mA anodaler tDCS des rechten dlPFC, erhöht werden. Der rechte dlPFC scheint somit auch neuroanatomisch zentral bei der Rekrutierung kognitiver Kontrolle beteiligt zu sein. Zum anderen liefert die Studie liefert zusätzliche Evidenz, dass psychophysiologische Prozesse bei Personen mit BES grundsätzlich veränderbar und modifizierbar sind und sie für den klinischen Alltag nutzbar sein könnten. Um klinische Relevanz eines tDCS gestützten kognitiven Trainings abschätzen zu können, bedarf es jedoch randomisierter-kontrollierter klinischer Studien, die systematisch diesen Effekt untersuchen. Erste Befunde aus der Pilotstudie, die eine Verringerung der selbstberichteten Essanfälle gefunden

haben, erscheinen jedoch bereits vielversprechend, wenn auch die Wirkweise und der zugrundeliegende Mechanismus mit den erhobenen Daten nicht eindeutig erklärbar waren.

Um nun die Brücke zu schlagen und eine Verbindung zwischen dem Einsatz neuer Technologien wie der VR und neuen Möglichkeiten zum Einsatz in der Diagnostik und Behandlung der BES herzustellen, wurde eine letzte Studie konzipiert. Die Studie bestand aus zwei Messzeitpunkten, die im Abstand von mindestens 6 Wochen stattfanden. Alle Probanden in dieser Studie wurden im Rahmen einer randomisierten-kontrollierten klinischen Studie (engl. randomized controlled trial RCT) rekrutiert und hatten somit zum ersten Messzeitpunkt eine diagnostizierte BES. In dem RCT (https://clinicaltrials.gov/ct2/show/study/NCT04572087) absolvierten die Patienten ein kognitives Training zur Modifikation von Impulsivität und verringerter Inhibitionsfähigkeit gegenüber Nahrungsreizen, wie sie auch bei Max, Plewnia, et al., 2021 verwendet worden ist. Zusätzlich erhielt die Experimentalgruppe eine anodale verum-Stimulation (2 mA) des rechten dlPFC, während die Kontrollgruppe lediglich eine Placebo-Stimulation erhielt. Die Probanden durchliefen an beiden Messzeitpunkten das in Max, Schroeder, et al. (2021) in der VR an Probanden ohne BES validierte neue experimentelle Paradigma. Daneben wurde Psychopathologie der BES, nahrungsbezogene und generelle Impulsivität, sowie Verlangen nach Essen über Fragebögen und semi-strukturierte klinische essstörungsspezifische Interviews operationalisiert. Durch die Teilnahme an dem RCT ist von einer Verbesserung der Symptomatik zum zweiten Messzeitpunkten auszugehen. Da die BES unter anderem durch erhöhte nahrungsbezogene Impulsivität und verringerte kognitive Kontrolle gekennzeichnet ist, sollte sich eine impulsivere, also schnellere Interaktion mit Nahrungsreizen im Vergleich zu Bürogegenständen zeigen. Darüber hinaus konnte bereits gezeigt werden, dass die Symptomatik eng mit kognitiven und behavioralen Verzerrungen zusammenhängt, sodass eine Veränderung bei der manuellen Interaktion mit Nahrungsmitteln in der VR im Allgemeinen, aber auch in Relation zum Ausmaß der Veränderung in der Symptomatik zu erwarten ist (Brockmeyer et al., 2019; Schmitz & Svaldi, 2017). Es zeigte sich zu beiden Messzeitpunkten eine schnellere Erkennung von Essen im Vergleich zu Bürogegenständen und eine schnellere nachfolgende Initiierung eines

Annäherungsverhaltens gegenüber Essen als bei Bürogegenständen. In einer zweiten Phase zeigte sich, dass nach der Initiierung des Annäherungsverhaltens das Essen jedoch langsamer eingesammelt wurde als die Bürogegenstände. Das langsamere Einsammeln von Essen lässt sich möglicherweise durch aversive motivationale Prozesse erklären. Die Nahrungsreize könnten von Patienten als etwas Problematisches, Beschämendes identifiziert worden sein, was dann ein beschleunigtes Einsammeln des entsprechenden Gegenstands verhinderte. Beide Verhaltensmuster zeigten sich sowohl zum ersten als auch zum zweiten Messzeitpunkt, obwohl sich die spezifische Psychopathologie der BES vom ersten zum zweiten Messzeitpunkt signifikant verbesserte. Bezüglich der klinischen Validität der Aufgabe fanden sich keine signifikanten Zusammenhänge zwischen der manuellen Interaktion mit Essen in der VR und der Psychopathologie, der generellen Impulsivität, dem Essverhalten oder dem Verlangen nach Essen. Auch intraindividuelle relative Veränderungen dieser Marker vom ersten zum zweiten Messzeitpunkt standen nicht in Beziehung zu den intraindividuellen relativen Veränderungen in der manuellen Interaktion mit Essen. Zusammenfassend lässt sich sagen, dass die Aufgabe differentielle Effekte in der Interaktion mit Essen aufzeigen konnte: Eine schnelle und impulsive erste Phase beim Erkennen von Essen und der nachfolgenden Annäherungsinitiierung, und eine langsamere zweite Phase beim Einsammeln von Essen. Dies deckt sich mit den Befunden aus der ersten Studie mit gesunden Probanden ohne BES, die ein ähnliches Interaktionsmuster mit Essen in der VR zeigten. Zwar ist ein Vergleich zwischen diesen beiden Gruppen post-hoc nicht mehr möglich aufgrund des fehlenden demographischen Matchings und der Optimierungen in der Physik der VR, dennoch scheint die Aufgabe zu insensitiv zu sein, um zwischen Leuten mit BES und ohne BES differenzieren zu können. Da keine Zusammenhänge zwischen dem manuellen Interaktionsverhalten mit Essen und den Markern der Psychopathologie der BES, der generellen Impulsivität, des Essverhaltens und dem Verlangen nach Essen zu beobachten waren, ist die Aussagekraft bezüglich der klinischen Validität dieser Aufgabe eingeschränkt und unterstützt nicht die Annahme des netzwerk-bezogenen Reduktionismus der BES in diesem spezifischen VR-Paradigma. Weitere objektive Marker vorrangig aus dem Bereich der Psychophysiologie (fNIRS, EEG, MRT) zur Diagnostik und Operationalisierung impulsbezogener

Störungen wie die der BES wären für weitere Studien wünschenswert. So könnten sowohl motivationale Prozesse aber auch neurophysiologische Maße, die durch das EEG oder fNIRS messbar sind, weitere Folgerungen für zugrundeliegende Prozesse, die sowohl zu der Entstehung aber auch zur Aufrechterhaltung der BES beitragen, zulassen.

6.1. Einordnung der Studienergebnisse

Ziel der vorliegenden Arbeit war es, den Erkenntnisstand zu kognitiven Verzerrungen und deren zugrunde liegenden neuronalen Mechanismen bei Nahrungsstimuli zu erweitern. Aus diesen Befunden sollten neue klinische Implikationen sowohl für die Diagnostik als auch für effektivere Therapieansätze bei der BES (auf reduktionistischen Ansätzen basierende kognitive Trainings) abgeleitet werden. In der ersten Arbeit (Max, Schroeder, et al., 2021) konnten in einem neuen experimentellen Paradigma Ergebnisse gefunden werden, die sich in bereits existierende behaviorale und neuronale Modelle einordnen lassen. So wird grundlegend von zwei verschiedenen, sich gegenseitig regulierenden Systemen ausgegangen, nämlich einem impulsiven und einem reflektierenden System (Metcalfe & Mischel, 1999; Strack & Deutsch, 2004). Gerade ein schwaches reflektierendes System scheint hierbei eine zentrale Rolle im Bereich von Essverhalten zu spielen, da dies zu impulsivem und enthemmtem Essverhalten führt, während ein starkes reflektierendes System nicht zwangsläufig zu weniger impulsivem Essverhalten führt (Honkanen, Olsen, Verplanken, & Tuu, 2012). Die Rolle eines impulsiven und reflektierenden Systems bedarf jedoch empirischer Validierung. In der ersten Studie (Max, Schroeder, et al., 2021) konnten Hinweise auf die Existenz eines dualen Systems bestehend aus einem impulsiven und reflektierenden System gefunden werden. So wurden in einer frühen Phase von Aufmerksamkeitsprozessen eine schnellere Erkennung und Kategorisierung von Essen gefunden, was für die Aktivierung eines impulsiven Systems spricht. Dieser Befund fand sich auch in der klinischen Stichprobe mit Patienten mit diagnostizierter BES wieder. In einer späteren Phase überwog jedoch das reflektierende System, wodurch es zu einer langsameren manuellen Interaktion mit den Nahrungsreizen kam. Möglicherweise wurde nach den frühen impulsiven Aufmerksamkeitsprozessen die von Friese, Hofmann & Wiers (2011) postulierte Selbstkontrolle aktiver, wodurch es zu einer langsamen Interaktion mit dem Nahrungsmittel kam. Da es sich um eine Stichprobe ohne (Lifetime-)Essstörungen handelte, könnte es sich hierbei um einen protektiven Mechanismus handeln, der bei Personen mit BES und damit verbundenem Kontrollverlust bei Essverhalten aufgrund erhöhter essensbezogener Impulsivität nicht vorhanden ist (Giel, Teufel, et al., 2017). Interessanterweise zeigte sich jedoch genau dieses Verhaltensmuster

auch bei den Patienten mit BES und zwar unabhängig davon, ob die essensspezifische Psychopathologie zum ersten Messzeitpunkt stärker ausgeprägt war als zum zweiten Messzeitpunkt (Max, Schag, et al., in preparation). Da in der Gruppe der Personen mit BES nicht von einer erhöhten Selbstkontrolle bereits zum ersten Messzeitpunkt auszugehen ist, könnten aversiv motivationale Prozesse diesem Verhaltensmuster zugrunde liegen, d.h. der Nahrungsreiz wurde nach einem spontanen Handlungsimpuls als problematisch identifiziert und das Einsammeln ebenjenes problematischen Gegenstands wurde verlangsamt (Field et al., 2016).

Auf neuronaler Ebene konnten in der Stichprobe ohne BES vorrangig Hinweise auf ein aktives Essensbewertungs-Netzwerk gefunden werden. Sofern Nahrungsstimuli als Zielstimulus definiert worden sind, war eine starke Aktivität vor allem im rechten dlPFC zu beobachten, die zudem auf Verhaltensebene ausschließlich mit einem beschleunigten Prozess des Erkennens, Kategorisierens und der Initiierung eines Annäherungsverhaltens zusammenhing. Die Evaluierung und das Erkennen des Nahrungsreizes führten zu einer Aktivierung im OFC, von dem die verarbeiteten hedonischen Werte des Essens an den dlPFC weitergeleitet wurden (Camus et al., 2009; Killgore et al., 2003; Morris & Dolan, 2001; Petrides & Pandya, 1999). Da es sich bei der Stichprobe um eine Stichprobe ohne Essstörungen handelte, sollten andere neuronale Prozesse, bzw. die Funktionalität dieser neuronalen Prozesse im Unterschied zu Personen mit BES evident werden. Bei Personen mit BES ist eine Hypoaktivität des rechten dlPFC gerade bei Konfrontation mit Nahrungsstimuli als Resultat defizitärer Inhibitionsfähigkeit gefunden worden (Lavagnino et al., 2016; Lee et al., 2017; Veit et al., 2021). Die Studie von Max, Schroeder, et al. (2021) zeigt bei Personen ohne BES vorrangig eine erhöhte Aktivität im rechten dlPFC als Resultat eines aktivierten Essensbewertungsnetzwerks zur Evaluation spezifischer Valenzen von Nahrungsreizen. Ein Zusammenhang von rechtem dlPFC und Inhibitionsfähigkeit, wie er bei Personen mit BES zu finden war, schien bei Personen ohne BES nicht zu bestehen. Dies unterstützt die Annahmen, dass nicht nur hinsichtlich Neuroplastizität im Sinne von Hyper- oder Hypoaktivität zwischen Personen mit oder ohne BES differenziert werden muss, sondern sich auch die Funktionalität von neuronalen Aktivitätsmustern zwischen Personen mit und ohne BES unterscheidet.

Während gezeigt werden konnte, dass der rechte dlPFC bei Personen ohne BES vorrangig mit dem Grad der individuellen Aktivierung des Essensbewertungsnetzwerk zusammenhing, zeigt die Forschung bei Personen mit BES, dass der Grad der Aktivierung des rechten dlPFC meist mit der individuellen Inhibitionsfähigkeit zusammenhängt (Lavagnino et al., 2016; Lee et al., 2017; Veit et al., 2021).

Darüber hinaus wurden zum ersten Mal überhaupt die Unterschiede zweier verschiedener Medien systematisch untersucht. Der Mediumsvergleich (VR vs. Touchscreen) zeigte, dass möglicherweise die VR bei der Modellierung von körperbezogenen Kognitionen bei Nahrungsreizen dem 2D-Medium überlegen sein könnte. Dies zeigt, dass nicht nur unmittelbar körperbezogene Kognitionen wie beispielsweise bei Körperbildstörungen über Spiegelexpositionen (Griffen, Naumann, & Hildebrandt, 2018) erfasst werden können, sondern auch essensspezifische Kognitionen, abgebildet durch das Annäherungsverhalten der Hand im dreidimensionalen Raum. Es ist davon auszugehen, dass diese Unterschiede durch den erhöhten Freiheitsgrad der Bewegung und die entsprechend höhere Ähnlichkeit zu naturalistischem Verhalten bei der VR erklärt werden können. Aufgrund dieser Ergebnisse wurde daher auch die letzte Studie (Max, Schag, et al., in preparation) in der VR und dem neu etablierten experimentellen Paradigma konzipiert, um neue, innovative Optionen bei der Behandlung der BES aufzuzeigen. Dennoch muss an dieser Stelle vermerkt werden, dass der zugrundeliegende Wirkmechanismus, der die beiden verwendeten Medien hinsichtlich der Verhaltensmuster in der Interaktion mit Essen unterscheidet, nicht explizit mittels erhobener Fragebögen erklärt werden konnte, weshalb es gerade hier noch weiterer systematischer Forschung bedarf. Auch im Bereich der VR wäre eine weitere Optimierung der verschiedenen Parameter, wie beispielsweise der Grad des Realismus oder der Präsenz im Raum, also dem Gefühl, sich tatsächlich in dem virtuellen Raum ganzheitlich zu befinden, wünschenswert (Schuemie, Van Der Straaten, Krijn, & Van Der Mast, 2001).

Doch es sollten nicht nur kognitive Verzerrungen und deren zugrundeliegende neurophysiologische Prozesse bei Nahrungsmitteln in Stichproben mit und ohne BES untersucht werden, sondern auch Erkenntnisse bezüglich klinischer Implikationen, Ansätze für neue Interventionen und

Modulierbarkeit defizitärer Verhaltensinhibition bei Personen mit BES gewonnen werden (İnce et al., 2021; Max, Plewnia, et al., 2021). Zum einen konnte ein Zusammenhang zwischen dem Maß der generellen Inhibitionsfähigkeit und der Performanz in einer Verhaltensaufgabe, in der Nahrungsreize präsentiert wurden, gefunden werden, und zwar in der Richtung, dass eine stärker ausgeprägte Impulsivität mit schlechterer Inhibitionsfähigkeit einherging. Da keine Zusammenhänge von Inhibitionsfähigkeit in der Verhaltensaufgabe mit Maßen der Psychopathologie und essensbezogener Impulsivität gefunden werden konnten, deckt sich dieser Befund nicht komplett mit dem Modell, dass eine zentrale Facette der BES die essensbezogene Impulsivität darstellt (Giel, Teufel, et al., 2017), sondern deutet vielmehr darauf hin, dass ein übergeordneter Faktor von Impulsivität bei der BES eine zentrale Rolle spielt. Betrachtet man Komorbiditäten mit anderen impuls-gestörten Krankheitsbildern, zeigt sich eine hohe Überlappung, was dafür spricht, dass Personen mit BES nicht nur in Bezug auf Essen impulsiver sind, sondern vielmehr Impulsivität als ein genereller Faktor erhöht ist. So zeigten laut einer Studie 26% der Kinder mit ADHS Verhalten von Essanfällen (Reinblatt, 2015). Auch die Lebenszeitprävalenz für eine stoffgebundene Abhängigkeit liegt bei Personen mit BES bei 19.9% und Personen mit BES haben gegenüber Personen ohne BES ein 1.5-fach erhöhtes Risiko, eine stoffgebundene Abhängigkeit zu entwickeln (Bogusz et al., 2021). Jedoch zeigte sich in der Studie von Max, Schag, et al. (in preparation), dass die Verbindung von Verhaltensmustern in der Interaktion mit Essen keine Zusammenhänge mit Markern der Psychopathologie der BES, der generellen und nahrungsbezogenen Impulsivität oder dem Verlangen nach Essen ergaben. Dies deckt sich mit vielen Befunden, die zeigen, dass möglicherweise die Außenvalidität von Verhalten in einem Laborsetting mit selbstberichteten Fragebögen oder klinischen Interviews nicht gegeben ist (Sharma et al., 2014). Was sich jedoch validieren ließ, sind die zugrundeliegenden neuronalen Prozesse der veränderten Inhibitionsfähigkeit bei Personen mit BES. So zeigten sich veränderte ERPs bei falschen Antisakkaden (Fehlern) gegenüber korrekten Antisakkaden, was wiederum auf veränderte neuronale und damit defizitäre Prozesse bei der Inhibitionsfähigkeit bei Nahrungsstimuli schließen lässt (İnce et al., 2021). Da diese veränderten ERPs nicht systematisch mit einer gematchten Kontrollgruppe verglichen worden sind,

lassen sich Verbindungen zur Psychopathologie nur begrenzt herstellen, zumal auch hier vorrangig stärkere Assoziationen mit genereller Impulsivität als mit der Psychopathologie der BES zu beobachten waren. Dennoch zeigte sich, dass sich ein Marker des ERP (P3) als Prädiktor für die Performanz zu späteren Messzeitpunkten interpretieren ließ. Die Tatsache, dass ein neurophysiologischer Marker spätere Performanz vorhersagen kann, stützt die Theorie individualisierter, neuro-phänotypischer Trainings im Sinne der reduktionistischen Theorie. So geht gerade der Neuroreduktionismus davon aus, dass psychische Erkrankungen ein Resultat veränderter psychophysiologischer und kognitiver Prozesse sind und dass durch die Reversibilität und Modifikation defizitärer psychophysiologischer und kognitiver Prozesse eine Verbesserung auf der Symptomebene einhergeht (Jacobson, 1993). In der durchgeführten Studie kann angenommen werden, dass besonders Personen, die bereits in der Baselinesitzung in der Lage waren, neuronale Ressourcen zu rekrutieren, die möglicherweise in Verbindung zu kognitiver Kontrolle stehen, auch stärker von einem solchen kognitiven Training profitieren könnten. Wenn man davon ausgeht, dass der Schweregrad der Erkrankung mit einer verringerten Fähigkeit neuronale Ressourcen zu rekrutieren, einhergeht, so lässt ich daraus schlussfolgern, dass Personen, die leicht- oder mittelgradig an der BES erkrankt sind, stärker von einem kognitiven Training profitieren könnten und dies somit möglicherweise auch schon als Präventionsmaßnahme zur Abwendung einer BES eingesetzt werden könnte.

Die Effektivität eines solchen kognitiven Trainings basierend auf der neuroreduktionistischen Grundidee kann durch die Befunde der neuromodulatorischen Effekte durch das tDCS gestützt werden (Max, Plewnia, et al., 2021). So konnte die Performanz in einer Verhaltensaufgabe zur Inhibition gegenüber Nahrungsreizen durch 2 mA anodale tDCS des rechten dlPFC verbessert werden, d.h. die Inhibitionsfähigkeit wurde durch eine erhöhte Erregbarkeit der kortikalen Bereiche gesteigert. Eine anzunehmende Hypoaktivität des rechten dlPFC bei Personen mit BES konnte somit durch die tDCS kompensiert werden, was zu erhöhter kognitiver Kontrolle und der damit verbundenen verbesserten Inhibitionsfähigkeit führte. Dies deckt sich mit den wenigen Befunden, die im Bereich der BES und tDCS gemacht wurden (Burgess et al., 2016). Diese Befunde stützen zudem die Annahme, dass der dlPFC eine zentrale Rolle bei der

kognitiven Kontrolle spielt und die kognitive Kontrolle über nicht-invasive Hirnstimulation kausal durch Modulation der Erregbarkeit kortikaler Bereiche erhöht werden kann. Darüber hinaus konnte ein klinischer Effekt im Sinne einer Reduktion der selbstberichten Essanfälle innerhalb des Zeitraums der Pilotstudie gefunden werden, der jedoch losgelöst von neuromodulatorischen Prozessen des tDCS zu sein scheint. Auch dieser klinische Effekt deckt sich mit bereits durchgeführten kognitiven Trainings zur Modifikation von kognitiven Verzerrungen bei der BES (Brockmeyer et al., 2019; Giel, Speer, et al., 2017). Aus reduktionistischer Sicht können somit kognitive Verzerrungen bei der BES aus zwei Perspektiven modifiziert werden. Zum einen auf einer Verhaltensebene, d.h. durch gezieltes Training einer Exekutivfunktion, und zum anderen auf einer neuronalen Ebene, d.h. durch Veränderung neuronaler Plastizität und Interkonnektivität. Diese Veränderung neuronaler Plastizität und Interkonnektivität kann auf der einen Seite durch gezieltes Training, also auf der Verhaltensebene, hervorgerufen werden, aber auch zusätzlich durch neuromodulatorische Techniken wie die tDCS unterstützt werden. Kombiniert man diese beiden Ansätze aus Training und Neuromodulation sollten sich additive Effekte ergeben, da das kognitive Training ebenfalls Veränderungen in der Neuroplastizität hervorrufen sollte, was dann wiederum durch die Neuromodulation zusätzlich unterstützt werden würde. An dieser Stelle ist jedoch festzuhalten, dass es zu Aussagen hinsichtlich der klinischen Effektivität zur Behandlung der BES mithilfe von kognitiven Trainings gestützt durch tDCS einer klinisch randomisierten-kontrollierten Studie bedarf. Die Pilotstudie zeigte vorrangig kognitive Verzerrungen und die zugrundeliegenden neuronalen Mechanismen bei Personen mit BES, sowie einen vielversprechenden Ansatz eines solchen Trainings zur Behandlung BES-spezifischer Symptome hinsichtlich der Reduktion von Essanfällen.

Mit der Validierung eines neuen experimentellen Paradigmas in der VR sollte an dieser Stelle eine Brücke geschlagen werden, um innovative Ansätze zur Behandlung von BES aufzeigen zu können. Durch den hohen Grad an Immersion, also dem Gefühl in der virtuellen Realität tatsächlich integriert zu sein, die die VR bietet, könnten Aufmerksamkeits- und Verhaltensverzerrungen bei Nahrungsreizen möglicherweise sensitiver aufgedeckt werden (Brown & Cairns, 2004). Tatsächlich scheint jedoch dieses spezifische experimentelle Paradigma von Max, Schag, et al.

(in preparation) noch zu insensitiv zu sein, um differentielle Effekte manueller Interaktion mit Essen bei Patienten mit Essstörung erkennbar zu machen. Es konnten Verhaltensmuster aus der Pilotstudie mit gesunden Probanden repliziert werden, jedoch veränderten diese sich nicht mit einer veränderten Psychopathologie der BES, die durch die Teilnahme an einer störungsspezifischen Behandlung im Rahmen eines RCT hervorgerufen wurde. Auch wenn der Schweregrad der BES zum zweiten Messzeitpunkt abnahm, veränderte sich nicht das Interaktionsmuster mit Nahrungsreizen in der VR. Fehlende Effekte könnten auch an der vergleichsweise geringen Stichprobengröße von 31 Patienten festgemacht werden oder an den kleinen Effektstärken, die hierbei zu erwarten gewesen wären. Diese Befunde stehen im Kontrast zu reduktionistischen Ansätzen, die verschiedene Facetten auf Phänomenebene (z.B. Verhalten, Psychophysiologie, Biomarker) und auf Symptomebene (z.B. spezifische klinische Symptome oder eine klinisch relevante psychische Erkrankung) als eng verwoben sehen und nach welchen eine Veränderung auf der Phänomenebene mit einer Veränderung auf der Symptomebene einhergehen sollte. Fehlende beobachtbare Zusammenhänge könnten jedoch mannigfaltige Ursachen haben. Zum einen könnte es an einem zu unspezifischen und unpassenden experimentellen Paradigma liegen, zum anderen könnte der Zusammenhang von Symptomebene und Phänomenebene über andere Faktoren, die nicht im Rahmen der Studie berücksichtigt wurden (bspw. motivationale Prozesse), moduliert werden. Eine Ausweitung der Erfassung verschiedener Marker auf Phänomenebene und eine quantitative Operationalisierung der Reziprozität der verschiedenen Marker im Rahmen einer Netzwerkanalyse erscheinen hierbei erfolgsversprechend, um ein tieferes Verständnis zwischen Symptom- und Phänomenebene zu erhalten (Borgatti, Mehra, Brass, & Labianca, 2009). Tatsächlich gibt es bereits auch erste Ansätze der Netzwerk-Analyse bei Essstörungen, jedoch beschränken sich diese vorrangig auf andere Essstörungen wie die Bulimia Nervosa (Levinson, Vanzhula, Brosof, & Forbush, 2018) oder nicht weiter spezifizierte Essstörungen (DuBois, Rodgers, Franko, Eddy, & Thomas, 2017; Olatunji, Levinson, & Calebs, 2018; Smith et al., 2018). Eine Netzwerk-Analyse bei Personen mit BES zeigte, dass die Überbewertung der Figur und des Gewichts eine zentrale Rolle als Facette der BES spielt und somit als diagnostische Marker neben den bereits existierenden

diagnostischen Kriterien der BES aufgenommen werden sollten (Wang, Jones, Dreier, Elliott, & Grilo, 2019). Limitierend bei diesen Netzwerk-Analysen ist vorrangig die Tatsache, dass ausschließlich Daten aus semi-strukturierten Interviews verwendet wurden und nicht weitere objektive, quantitative Daten wie psychophysiologische Maße oder Marker auf der Verhaltensebene in experimentellen Paradigmen. Durch Marker der Psychophysiologie oder der Verhaltensebene könnten mehr Erkenntnisse gewonnen werden, wie neue, innovative Ansätze zur Behandlung der BES konzipiert werden sollten. Dadurch könnten Ansätze kognitiver Trainings durch Modifikation verzerrter Kognitionen, Modifikation von Neuroplastizität mittels Hirnstimulation oder eine Kombination aus beiden dazu genutzt werden, um klassische, bereits existierende Verfahren wie die der Verhaltenstherapie zu augmentieren.

6.2. Limitationen und Ausblick

In dieser Arbeit wurde der Fokus neben den psychophysiologischen Maßen auf verschiedene kognitive Aspekte bei der Verarbeitung von Nahrungsreizen gelegt, vorrangig auf die Geschwindigkeit der Kategorisierung (Erkennen des Essensobjekts), die Inhibitionsfähigkeit (Initiierung einer Antisakkade bei Präsentation von Essen) und die Impulsivität (Einsammeln des Essensobjekts). Andere kognitive Aspekte, die als Prädiktor, Mediator oder Moderator von Therapieerfolg fungieren, konnten hierbei nicht vollständig abgedeckt werden und wären für weitere Arbeiten von Interesse. Darunter zählen unter anderem restriktives Essen, Figur- und Gewichtssorgen (Iacovino, Gredysa, Altman, & Wilfley, 2012). Zur Erforschung dieser kognitiven Prozesse, die diese Themenbereiche abdecken, bedarf es jedoch neuer experimenteller Paradigmen und anderer Stimulusmaterialien (z.B. verschiedene Körpermodelle im Sinne virtueller Avatare, die direkt in der VR implementiert und modelliert werden können). Auch verhaltenstherapeutische Interventionen im Sinne einer kognitiven Umstrukturierung mit Fokus auf Figur- und Gewichtssorgen im Rahmen von Nahrungsmittelexposition in der VR, die bereits als wirksam nachgewiesen werden konnten (De Carvalho, Dias, Duchesne, Nardi, & Appolinario, 2017), erscheinen hier vielversprechend. Gerade die Möglichkeit, viele verschiedene Parameter bei verhaltenstherapeutischer Exposition in einem sicheren Umfeld zu manipulieren

(Gestalt des Essens, Gestalt der Umgebung), bietet die Verwendung der VR als therapeutisches Tool. Dadurch, dass die VR im Laufe der Zeit immer kostengünstiger zu erwerben ist und mittlerweile auch über Handysysteme zugänglich ist, besteht zudem die Perspektive, kognitive Trainings in der VR als Home-Treatment anzubieten. Dies könnte dann bis zur Aufnahme einer Psychotherapie überbrückend von betroffenen Leuten mit BES genutzt werden. Jedoch muss an dieser Stelle festgehalten werden, dass in dieser Arbeit das experimentelle Paradigma zwar differentielle Effekte bei der manuellen Interaktion mit Essen zeigte, jedoch in keinem Zusammenhang zur Psychopathologie der BES stand, wodurch auf dieser Grundlage zunächst noch kein kognitives Training konzipiert werden kann. Die Erforschung besserer Konstruktvalidität zwischen verschiedenen objektiven Maßen der Impulsivität und Psychopathologie im Sinne von grundlagenorientierter Forschung sollte hier noch einmal einen besonderen Stellenwert erhalten. Fände man einen Zusammenhang von Verhaltens- und Symptomebene, könnte man die Wirksamkeit zur Behandlung der BES mit einem kognitiven Training in der VR durch die Modifikation der Verhaltensebene im Sinne des Reduktionismus untersuchen. Um diesen Schritt zu gehen, bedarf es aber eines experimentellen Paradigmas, das enger an die Psychopathologie der BES geknüpft ist.

Die Ansätze zur Entwicklung eines neuromodulationsgestützten kognitiven Trainings mit einem bereits etablierten experimentellen Paradigma, einer nahrungsspezifischen Antisakkadenaufgabe, erscheinen vielversprechend. Trotzdem es größerer Stichproben als der vorliegenden bedarf, um eine höhere Validität und Repräsentativität zu erzielen, konnten auch im Sinne eines multimodalen Ansatzes verschiedene zugrundeliegende Mechanismen, die mutmaßlich im Sinne des Reduktionismus zur Entstehung und Aufrechterhaltung der BES beitragen, identifiziert werden. So könnte auch der psychophysiologische Marker im EEG als Maß der Inhibitionsfähigkeit (P3) für ein Neurofeedbacktraining genutzt werden. Erste Versuche, Neurofeedbacktraining als klinische Intervention zu nutzen, sind hierbei vielversprechend und wirken sich positiv auf die Reduktion von Essanfällen und der generellen Psychopathologie aus (Blume, Schmidt, Schmidt, Martin, & Hilbert, 2021). Mit Fokus auf die Kombination aus Neuromodulation und kognitivem Training kann festgehalten werden, dass bereits

klinisch relevante Effekte nach der ersten Sitzung ohne tDCS zu beobachten waren. Dies deckt sich empirisch mit den Befunden, dass bereits 65-70% der Patienten mit BES innerhalb der ersten 4 Sitzungen eine Reduktion von Essanfällen zeigen und bereits Kurzinterventionen effektiv zu sein scheinen (Iacovino et al., 2012). Im Sinne einer Verbesserung der Nachhaltigkeit dieser klinisch relevanten Effekte scheint jedoch die Kombination aus kognitivem Training und Neuromodulation vielversprechend zu sein, gerade um Neuroplastizität langfristig zu modifizieren und aufrechtzuerhalten. Da gerade auch nur rund 50% der Patienten mit BES langfristig abstinent von Essanfällen bleiben, muss der Fokus auf der Nachhaltigkeit der klinischen Effekte liegen (Deutsche Gesellschaft für Essstörungen (DGESS), 2018). Dafür wurde bereits eine Intervention in Form eines tDCS-gestützten kognitiven Trainings konzipiert, welche vorsieht, innerhalb eines zweiwöchigen Trainings mit 6-Sitzungen den Zusatzeffekt von 2mA anodaler tDCS des rechten dlPFC gegenüber placebo-Stimulation zu untersuchen (Giel, Schag, Martus, Max, & Plewnia, 2022). Gerade die anhaltenden klinischen Effekte vier und zwölf Wochen nach Beendigung des Trainings bilden das zentrale Studienergebnis. Erkenntnisse aus dieser Studie könnten neue Möglichkeiten bei der Behandlung der BES aufzeigen. Niederschwelligere Angebote wie ein selbst-durchzuführendes kognitives Training und einfach anzubringende Elektroden, könnten einen positiven klinischen Effekt auf die Symptomatik der BES haben und somit auch den Weg bis zur Aufnahme einer Psychotherapie überbrücken oder bestenfalls auch gänzlich ersetzen.

6.3. Fazit

Um kognitive Trainings zur Behandlung von Essstörungen attraktiver und auch interindividuell effektiver zu gestalten, sollte die vorliegende Arbeit ausreichend gezeigt haben, dass weitere multimodale Ansätze verfolgt werden sollten. Viele einzelne Bestandteile der erforschten Teilbereiche zeigen auf, dass die Effektivität von Interventionen zusätzlich gesteigert werden kann. So scheinen zum einen Personen mit bestimmten Ressourcenallokationen psychophysiologischer Marker im EEG, vorrangig die der P3, besonders von einem neuromodulationsgestützten Training profitieren zu können. Des Weiteren konnte gezeigt werden, dass die erhöhte Intensität applizierter Neuromodulation, in diesem

Fall 2mA anodale tDCS des rechten dlPFC, einen positiven Effekt auf die Inhibitionsfähigkeit bei der BES haben kann. Gerade die Kombination aus Neuromodulation und kognitivem Training scheint hierbei auch bei der Behandlung der BES vielversprechend. So zeigte sich bereits ein schnell eintretender klinischer Effekt hinsichtlich der Reduktion von Essanfällen.

Weiterhin konnte gezeigt werden, dass die VR gegenüber anderen Medien wie einem 2D-Touchscreen überlegen ist, nahrungsbezogene Kognitionen abzubilden. Dabei scheint wohl gerade der Bereich der körperbezogenen Kognitionen der zugrundeliegende Mechanismus zu sein. Zudem zeigte sich, dass sich in neuen Technologien wie der VR durch ein darauf ausgerichtetes experimentelles Paradigma nahrungsbezogene differentielle Effekte in der manuellen Interaktion mit Essen als spezifische Verhaltensmuster niederschlagen, die auf verschiedene kognitive Phasen rückschließen lassen und die Annahme eines Dualismus von einem impulsiven und einem reflektierenden System unterstützen. Eine Interkonnektivität zwischen der frühen kognitiven Verarbeitung und dem rechten dlPFC scheint gegeben zu sein und liefert Evidenz für ein Essensbewertungssystem, bei dem Nahrungsvalenzen bereits in einer frühen Phase des Erkennens und Kategorisierens verarbeitet werden. Multimodale Ansätze zur Erfassung motivationaler, psychophysiologischer und kognitiver Prozesse zur objektiven Diagnostik und vor allem zum Einsatz von klinischen Interventionen bei der BES sollten weiterhin verfolgt werden, um ein ganzheitliches Bild der BES auf Symptom- und Verhaltensebene im Sinne der reduktionistischen Ansätze zu erhalten. Dies kann eine Grundlage sein, um entsprechend interindividuell angepasste Interventionen zu gestalten, die zur Erzielung eines Maximums an Behandlungseffektivität am vielversprechendsten erscheinen.

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8. Anhangsverzeichnis

9. Anhang

9.1. Erklärungen zum Anteil gemeinschaftlicher Veröffentlichungen

Erklärung nach § 5 Abs. 2 Nr. 8 der Promotionsordnung der Math.-Nat. Fakultät
-Anteil an gemeinschaftlichen Veröffentlichungen-
Nur bei kumulativer Dissertation erforderlich!

Declaration according to § 5 Abs. 2 No. 8 of the PhD regulations of the Faculty of Science
-Collaborative Publications-
For Cumulative Theses Only!

Last Name, First Name: Max, Sebastian M.

List of Publications

1. Max, S.M., Plewnia, C., Zipfel, S. *et al.* (2021) Combined antisaccade task and zranscranial direct current stimulation to increase response inhibition in binge eating disorder. *Eur Arch Psychiatry Clin Neurosci* 271, 17–28. https://doi.org/10.1007/s00406-020-01164-5

2. Max, S.M., Schroeder, P.A., Blechert, J. *et al.* (2021) Mind the food: behavioural characteristics and imaging signatures of the specific handling of food objects. *Brain Struct Funct* 226, 1169–1183. https://doi.org/10.1007/s00429-021-02232-9

3. İnce B., Max S.M., Plewnia, C. *et al.* (2021) A pilot event-related potentials study on mechanisms underlying a tDCS-enhanced food-specific response inhibition task for patients with binge eating disorder. *Front Psychol* 12, 721672. http://doi.org/10.3389/fpsyg.2021.721672

4. Max, S.M., Schag, K., Giel, K.E., & Plewnia, C. (in preparation) Behavioural biases in the interaction with food objects in virtual reality and its clinical implication for the binge eating disorder.

Nr.	**Accepted publication yes/no**	**List of authors**	Position of candidate in list of authors	Scientific ideas by the candidate (%)	Data ge-neration by the candidate (%)	Analysis and Interpretation by the candidate (%)	Paper writing done by the candidate (%)
1	yes	Max, Plewnia, Zipfel, Giel, Schag	First author	10	85	65	75
2	yes	Max, Schroeder, Blechert, Giel, Ehlis, Plewnia	First author	70	100	65	75
3	yes	İnce, Max, Plewnia, Leehr, Zipfel, Giel, Schag	Shared first author	10	85	50	40
4	no	Max, Schag, Giel, Plewnia	First author	50	100	75	75

9.2. Akzeptierte Publikationen

European Archives of Psychiatry and Clinical Neuroscience (2021) 271:17–28
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ORIGINAL PAPER

Combined antisaccade task and transcranial direct current stimulation to increase response inhibition in binge eating disorder

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Abstract

Binge eating disorder (BED) is associated with deficient response inhibition. Malfunctioning response inhibition is linked to hypoactivation of the dorsolateral prefrontal cortex (dlPFC), where excitability could be increased by anodal transcranial direct current stimulation (tDCS). Response inhibition can be assessed using an antisaccade task which requires supressing a dominant response (i.e. saccade) towards a newly appearing picture in the visual field. We performed a double-blind, randomised, placebo-controlled proof-of-concept-study in which we combined a food-modified antisaccade task with tDCS in people with BED. We expected task learning and modulatory tDCS effects. Sixteen people were allocated to a 1 mA condition, 15 people to a 2 mA condition. Each participant underwent the food-modified antisaccade task at three measurement points: baseline without stimulation, anodal verum and sham stimulation at the right dlPFC in a crossover design. The error rate and the latencies of correct antisaccades decreased over time. No tDCS effect on the error rate could be observed. Compared to sham stimulation, 2 mA tDCS decreased the latencies of correct antisaccades, whereas 1 mA tDCS increased it. Self-reported binge eating episodes were reduced in the 2 mA condition, while there was no change in the 1 mA condition. Participants demonstrated increased response inhibition capacities by a task learning effect concerning the error rate and latencies of correct antisaccades over time as well as a nonlinear tDCS effect represented by ameliorated latencies in the 2 mA and impaired latencies in the 1 mA condition. The reduction of binge eating episodes might indicate a transfer effect to everyday life. Given that the reduction in binge eating was observed before tDCS administration, this effect could not be the result of neuromodulation. Randomized clinical trials are needed to fully understand this reduction, and to explore the efficacy of a combined antisaccade and tDCS training for BED.

Keywords Antisaccade · Binge eating disorder · Cognitive control · Impulsivity · Response inhibition · Transcranial direct current stimulation

Introduction

Since 2013, binge eating disorder (BED) is a distinct eating disorder diagnosis in the Fifth Edition of the Diagnostic and Statistical Manual of Mental Disorders (DMS-V). The estimated prevalence rate BED is with 1–4% higher than those of other eating disorders, and BED has a severe impact on individuals' health and functioning level [1–3]. According to current treatment guidelines, the current treatment of choice is cognitive behavioural therapy (CBT). Unfortunately, only 50% of affected patients are fully remitted after CBT [4]. Thus, novel innovative treatments addressing the proposed underlying mechanisms of the disorder and targeting the brain directly, e.g. using neuromodulation techniques, could increase therapy benefit and remission rates in BED [5].

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BED is characterized by recurrent binge eating episodes without inappropriate compensatory behaviours which is a core characteristic of bulimia nervosa. During binge eating episodes, an experienced loss of control is reported. This loss of control is closely linked to food-related impulsivity, i.e. binge eating could be understood as impulsive eating behaviour [6]. Two important factors that characterize impulsivity are, (1) increased sensitivity to rewarding stimuli, and (2) increased rash and spontaneous behaviour or decreased response inhibition [7, 8]. An executive function to overcome or correct impulsive behaviour in favour of another reaction is cognitive control [9, 10]. Thus, cognitive control and impulsivity are overlapping constructs concerning response inhibition. An experimental approach to operationalize response inhibition is the antisaccade paradigm, a task where an automatic and highly dominant reflectory gaze movement towards newly appearing stimuli has to be suppressed and corrected [11, 12]. In a modified antisaccade task with food vs. neutral control stimuli, it has been shown that participants with BED had more problems in inhibiting saccades towards food stimuli compared to matched normal weight and individuals with obesity who did not have an eating disorder [13]. Moreover, first attempts to use this response inhibition paradigm as a training programme for patients with BED in three sessions using only food stimuli delivered promising results that such a training might support patients to reduce binge eating episodes [14].

On a biopsychological level, response inhibition is associated with the dorsolateral prefrontal cortex (dlPFC) [15, 16]. Specifically, the right dlPFC is involved in tasks in which response inhibition is needed to overcome impulsive prepotent actions, thus resulting in goal-directed behaviour [17, 18]. There is evidence that impaired response inhibition in people with BED is more prominent, but not restricted to food-specific stimuli and may reflect a generally decreased capacity for response inhibition [19, 20]. In particular, reduced neural activity in the dlPFC and associated malfunctioning in response inhibition were observed in people with BED [21]. In the current study, we aimed to combine the food-modified antisaccade task with non-invasive brain stimulation to directly target the underlying neural networks.

An effective tool to modulate neural activity associated with response inhibition and food processing is transcranial direct current stimulation (tDCS) [5, 22, 23]. Through anodal tDCS, cortical excitability can be facilitated by application of a weak current (1–2 mA) to the scalp [24]. In a sample without mental disorders, it has already been demonstrated that response inhibition can be modulated by tDCS [25]. In the domain of BED, the evidence of tDCS is very scarce, as most studies investigate the effects of tDCS on food-related craving in non-eating-disordered samples or samples with other eating disorders [5, 22]. To our knowledge, only one study focused on food-related craving (and not response inhibition) in patients with BED, where food craving and food intake could be reduced due to anodal tDCS to the right dlPFC [26]. In people with bulimia nervosa, tDCS decreased the self-reported urge to binge eat and increased self-regulatory control [27]. This supports the hypothesis of a hypoactivated response inhibition network in people with BED. However, the participants in these studies did not execute disorder-relevant tasks during stimulation. A direct combination seems very promising to draw a direct link between neural activity and behavioural outcomes.

In the present randomized, placebo-controlled, double-blind proof-of-concept-study, the systematic effect on response inhibition of anodal tDCS to the right dlPFC combined with the food-modified antisaccade task [14] in a sample with diagnosed BED was investigated. Findings of this pilot study will be used to develop a suitable training programme for patients with BED, e.g. to determine optimal stimulation parameters, and to investigate the expected underlying mechanisms concerning food-related impulsivity and cognitive control. In addition to expected learning effects elicited by the repeated execution of the food-modified antisaccade task, anodal tDCS should additionally compensate for hypoactivity of the right dlPFC in people with BED, thus resulting in improved performance in this task in comparison with sham stimulation. After a baseline measure at T0, sham and verum stimulations were randomized in counterbalanced order across measurement point T1 and T2. Further, participants were allocated to either a group that received 1 mA tDCS or 2 mA tDCS. As different stimulation intensities yield different and possible nonlinear effects [28, 29], those two stimulation intensities were compared to explore the optimal intensity of stimulation.

Taken together, we expect that the patients improved in the food-modified antisaccade task over the three measurement points independently of the allocated condition, i.e. the order of sham/verum stimulation and its intensity (1 mA vs. 2 mA) ("learning effect"). Concerning tDCS, we additionally expect that the participants improved under verum stimulation compared to sham stimulation ("tDCS effect"). Improvement means that the participants executed less wrong antisaccades and faster correct antisaccades. Further, we compare the tDCS effects of the two groups with 1 mA vs. 2 mA stimulation. As a clinical measure, we explore, if and how the participants changed in the frequency of binge eating episodes over time. Last, we expect positive associations between self-reported trait impulsivity and food-related impulsivity with the performance in the food-modified antisaccade task.

Methods

Participants

Participants were adults with normal weight or overweight/obesity (BMI > 20 kg/m^2) to exclude patients with restrictive eating patterns or subsyndromal anorexia nervosa and had to fulfil criteria for BED according to DSM-5 [30]. Exclusion criteria were: attention deficit hyperactivity disorder (ADHD), psychotic disorders, bipolar-I disorder, current alcohol or drug addiction, current suicidality, current pregnancy, current physical illness which influences weight or eating behaviour and unstable medication, neurological diseases, current medication with neuroleptics or benzodiazepines, current attendance to structured dieting programs, past bariatric operations, metallic implants in the head, eye diseases.

We included 31 participants in the first condition with 1 mA, but 15 were screening failures due to inappropriate self-reports concerning in- and exclusion criteria in a screening checklist that we realized at the diagnostics appointment (no BED: 8, ADHD: 4, bariatric surgery: 2, history of seizures: 1). Thus, they were discarded from the study and only those 16 patients who fulfilled in and exclusion criteria in the diagnostics session were randomised within the 1 mA condition to receive first sham and then verum tDCS or vice versa.

Based on the experiences from the 1 mA condition, we included a short screening on the phone concerning inclusion and exclusion criteria for the 2 mA condition. Thus, we included 18 participants in the 2 mA condition, where three subjects were excluded during diagnostics, (no BED: 2, ADHD: 1), so that 15 subjects were finally randomised within the 2 mA condition. The participants received a reimbursement for study participation. The study was approved by the ethics committee of the Medical Faculty Tübingen, Germany and all participants gave written informed consent.

Study design

This is a double-blind randomised placebo-controlled proof of concept study in a cross-over design (see Fig. 1). The intensity of the stimulation (1 mA vs. 2 mA) serves as a between-subject variable, as the participants were allocated to one specific stimulation intensity. The stimulation order (sham vs. verum) serves as a within-subject variable to which the participants got randomly assigned. If they received sham stimulation at the second study appointment (T1), they received verum stimulation at the third study appointment (T2) and vice versa. Counterbalancing of the stimulation order should minimize the influence of training effects.

Food-modified antisaccade task

In the food-modified antisaccade task, the participants were initially instructed to look at a fixation cross in the middle of the screen for 1250 ms in each trial as long as no picture was

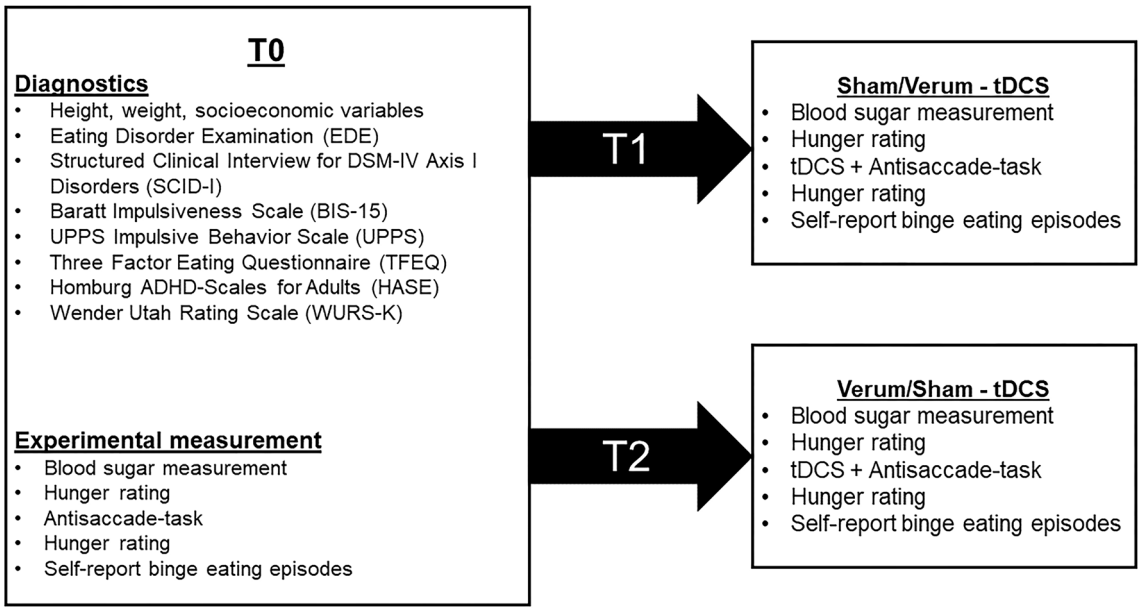

Fig. 1 An overview of the three sessions (T0, T1 and T2) and the assessed data. The allocation to the two stimulation conditions (verum and sham stimulation) was randomized, counterbalanced and double-blind

presented. After an interstimulus intervall (ISI) of 200 ms, a food picture was displayed randomly on the left or the right side of the screen for 1000 ms. As soon as the food picture was presented, the participants had to look as fast as possible on the opposite side of the screen. Each of the 40 food pictures was presented four times, counterbalanced on the left and the right sight on the screen, resulting in 160 trials. An exemplary trial is shown in Fig. 2.

Stimuli and stimulus presentation

40 coloured high-caloric food stimuli with a resolution of 400 × 295 pixels served as stimulus material. The stimuli were pretested in other studies concerning response inhibition in BED [14, 31]. The stimulus material was displayed on 15.6-inch laptop screen with a resolution of 1280 × 1024 pixels.

Apparatus

Eye tracking

Eye movements were recorded with SMI RED250mobile with a 250 Hz sampling rate, 0.4° gaze position accuracy, and iViewRed software. The mobile eye tracker, which was attached below the laptop screen, was placed 30 cm in front of the participant.

Eye movement data

Raw data were analysed with BeGaze 3.7 using the velocity-based default algorithms that define fixations and saccades. Data cleaning and composition of the output variables, i.e. trial classification (correct vs. error) and latencies were executed by MatLab R2017b. A trial was excluded from further analysis, if participants didn't look at the fixation cross at the onset of the trial and if data were not recorded due to technical problems. Saccades starting below 80 ms and above 900 ms were considered premature/delayed, thus getting excluded from further analyses. As a marker of response inhibition, the error rate (ergo prosaccades to the food stimulus) and the latencies of correct antisaccades were used. Whereas the error rate reflects decreased response inhibition skills [12], the latency of correct antisaccades is indicating faster goal-directed behaviour and gives insight into the needed effort in inhibiting a reflexive prosaccade [32, 33].

Transcranial direct current stimulation (tDCS)

Transcranial direct current stimulation (tDCS) was delivered by two 5 × 7 cm electrodes which were both prepared with Ten20 conductive paste (Weaver and Company, Aurora, CO, USA). tDCS was administered over a 20 min period using a battery-driven, constant-current stimulator (DC-STIMULATOR MC, NeuroConn GmbH, Ilmenau, Germany). The cathode was placed extracephalic on the left deltoid muscle, the anode was placed over F4 according to the international 10–20 system of electrode placement [34]. Using a unipolar tDCS montage, we aimed to exclusively target the right dlPFC with anodal stimulation [35]. After a fade-in of 5 s, the current reached either 1 mA or 2 mA depending on the assigned group. After 20 min, the current was faded out within 5 s. For sham stimulation, the parameters of fade-in and fade-out were the same, but the current was only applied for 46 s. This is considered as a valid placebo-control as perceived sensations on the skin (e.g. tingling) usually fade out in the first 30 s of tDCS [36]. As putting a unique 5-digit code for each participant activates either real or sham stimulation, the experimenter was blinded to the randomisation condition (sham vs. verum).

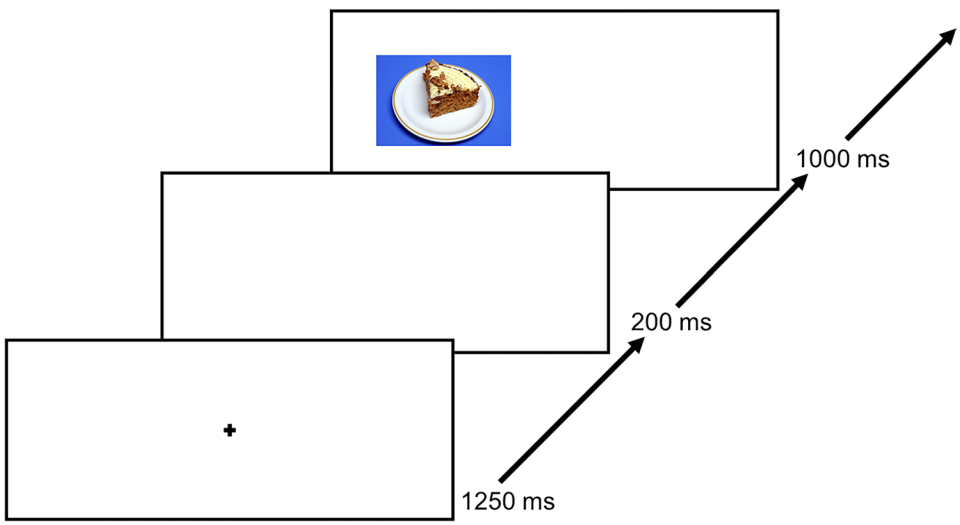

Fig. 2 An exemplary trial course. The trial starts with a 1250 ms lasting fixation. After an ISI with 200 ms, a food picture was presented for 1000 ms. Thereafter, the next trial starts again with a fixation

Questionnaires

Barratt impulsiveness scale (BIS-15)

The questionnaire assesses impulsivity as a personality trait operationalized by rapid, unplanned actions regardless of possible negative consequences. The questionnaire consists of three factors: non-planning, motor and attentional impulsivity. For the current study, only the total score was used which is a good marker of impulsivity and high internal consistency [37]. A higher total score indicates higher general impulsivity.

UPPS impulsive behaviour scale (UPPS)

The questionnaire measures and conceptualizes impulsivity with four facets: urgency, lack of premeditation, lack of perseverance, and sensation seeking. Urgency captures the tendency to undergo strong impulses mainly under the influence of negative affect. Premediation measures the tendency to act deliberately and consciously. Perseverance describes the ability to stay focussed on a boring or difficult task. Sensation seeking comprises the tendency to enjoy risky and exciting activities and openness for new experiences [38]. A higher score of the different subscales indicates either higher urgency, lower premeditation, lower perseverance or higher sensation seeking.

Three-factor eating questionnaire (TFEQ)

The questionnaire consists of three scales to conceptualize eating behaviour by behavioural, cognitive, and affective components. Restraint comprises strategic dieting behaviour, the ability of self-regulation and avoidance of fattening foods. Disinhibition refers to habitual, emotional, and situational susceptibility. The last component is hunger which comprises internal and external processing for hunger cues [39]. A higher score of the subscale indicates a higher extent of the eating behaviour component.

Procedure

An overview of the study appointments is depicted in Fig. 1. Between each of the three study appointments, there was a minimum temporal distance of 1 week to control for carry-over effects as this seems to be a sufficient wash-out period [40–42]. To control for circadian effects, participants came at the same time in the late afternoon/early evening for each study appointment. To hold homeostatic effects constant, the participants were instructed to fast at least 4 h before they arrived at the laboratory to be in a moderately hungry state while completing the tasks, as hunger increases food-related attentional and motivational processes [43]. Blood sugar levels were assessed as well as hunger levels at visual analogue scales ranging from 0 cm (not hungry) to 10 cm (extremely hungry).

At the diagnostics appointment at T0, height, weight and socioeconomic variables were assessed. To check in and exclusion criteria, we executed two structured interviews for current eating disorder diagnoses (EDE, [44] and SCID-I, [45]). To assess BED according to DSM-5, we slightly modified the German version of the EDE instead of DSM-IV in that way that an average of one binge eating episode per week within 3 months was necessary to diagnose BED instead of an average of two binge eating episodes per week within 6 months. To characterise the sample, participants filled out standardized questionnaires concerning impulsivity (BIS-15 [37]; UPPS Impulsive Behaviour Scale [38]), eating behaviour (TFEQ [39]) and ADHD (HASE [46]; WURS-K [47]) (see above). At the same appointment, the experimental baseline measurement with the food-modified antisaccade task was conducted. Afterwards, a self-report about the frequency of binge eating episodes in the last 7 days was filled out.

The following two experimental measurements at T1 and T2 were similar to T0 with the exception that additionally tDCS (verum/ sham) was applied. At T2, participants had to guess in a blinding check which session verum stimulation was applied and rated frequency as well as intensity of adverse events on a scale ranging from 1 (“not at all”) to 5 (“extremely”).

Data analysis and statistics

Behavioural data analysis

All statistical inferences were conducted on a significance level of 95%. The sample was compared in the two study conditions (1 mA vs. 2 mA) with t tests or Mann–Whitney U tests, if data were not normally distributed, and Chi square tests for binary data. Manipulation and blinding checks were executed with t tests.

Concerning eye tracking data, participants with less than 25 trials at T0 due to bad data quality (i.e. recording problems) were totally excluded ($N = 4$), so that $N = 15$ were analysed in the condition 1 mA and $N = 12$ in the condition 2 mA. To account for different datapoint contributions to the analysis, mixed models were calculated by the *lme4*-package of R [48]. To analyse the error rate, generalized linear mixed models were performed which return the logit of an error and transforms it into a probability. To analyse the latencies of correct antisaccades, linear mixed models were performed which return a numeric estimate for each included factor level. Two more participants in the condition 2 mA had to be excluded in the analysis on latencies of correct antisaccades, as they did not perform any correct saccades at T0 to

calculate a valid baseline covariate. To investigate stimulation-independent learning effects, the fixed effect of session (T0, T1, and T2) was tested in log-likelihood tests. Incorrect executed trials (see above) were excluded from the analysis, so that concerning the error rate, 7922 trials (61.13%), and concerning the latencies of correct antisaccades, 5013 trials (41.78%) could be analysed. To investigate stimulation-dependent effects, two fixed effects were tested: stimulation (verum vs. sham), intensity (1 mA vs. 2 mA). Only the trials of the two stimulation sessions (T1, T2) were analysed and an individual baseline performance was also included as a fixed effect to serve as a correction factor for learning effects. Concerning the error rate, 5146 trials (59.56%), and concerning the latencies of correct antisaccades, 3428 trials (42.85%) could be analysed.

The self-reported frequency of binge eating episodes in the last 7 days was analysed consistently with a linear mixed model including the session (T0, T1, T2) and the stimulation intensity (1 mA vs. 2 mA) as fixed effects.

Concerning all variables, post hoc contrasts within fixed effects were tested with the method of least-squares means [49] by the *lsmeans* package of R and adjusted by Tukey method. Cohen's *d* was used as a standardized effect-size measure [49]. As the eye tracking data were not normally distributed, Spearman's correlations between the BIS-15, UPPS and TFEQ and the eye tracking performance at T0 were executed.

Results

Sample characteristics

The sample characteristics are described in Table 1. The samples in the two study conditions did not differ from each other concerning the outcomes presented in Table 1 and additionally concerning blood glucose level, education, marital status and frequency of comorbid mental disorders.

Manipulation and blinding check

Blood sugar levels across all participants and measurement points were on average at 100.0 mmol/l (SD = 19.6) and rated hunger levels at 54.8 (SD = 19.1), which speaks for a moderately hungry state before each experimental measure as expected. The probability of the correctly guessed verum stimulation session was at chance level (55.56%), $t(26) = 0.57$, $p = 0.574$ and did not differ between groups, (1 mA = 60%; 2 mA = 50%), $t(25) = 0.50$, $p = 0.620$. Thus, a blinding of the participants overall can be assumed. None of the participants reported severe adverse events, but some light and already well-known adverse events were reported: 22 (81.5%) participants reported tingling of the electrodes

Table 1 Sample characteristics at baseline

	1 mA ($N = 15$)	2 mA ($N = 12$)	p
Age	35.7 (13.0)	40.6 (15.6)	0.52
Sex	1 m, 14 f	3 m, 9 f	0.18
BMI (kg/m^2)	32.1 (10.9)	33.8 (9.6)	0.67
Binge eating days in the last 4 weeks according to EDE	11.3 (5.7)	12.8 (7.8)	0.87
EDE total score	1.8 (.7)	2.0 (.9)	0.61
TFEQ disinhibition	11.3 (3.2)	11.6 (2.6)	0.78
TFEQ feelings of hunger	8.5 (2.7)	10.3 (2.2)	0.08
TFEQ cognitive restraint	7.9 (4.0)	6.1 (3.2)	0.19
BIS-15 total score	30.1 (7.1)	27.6 (2.6)	0.30
UPPS urgency	31.5 (5.8)	29.3 (4.6)	0.29
UPPS premediation	24.3 (4.3)	24.3 (3.2)	0.98
UPPS lack of perseverance	19.9(2.9)	22.3 (3.6)	0.07
UPPS sensation seeking	30.9 (8.3)	29.8 (9.3)	0.73

BIS-15 Baratt Impulsiveness Scale *EDE* eating disorder examination; *f* female; *m* male; *TFEQ* three-factor eating questionnaire; *UPPS* UPPS Impulsive Behaviour Scale

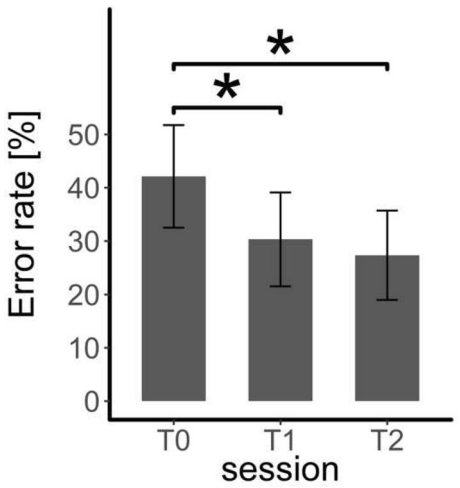

Fig. 3 The error rate (mean, standard error) at each study appointment (T0, T1 and T2). * $p < .05$

($M = 2.52$), 8 (29.6%) tingling on the head ($M = 1.41$), 12 (44.4%) itching ($M = 1.78$), 8 (29.6%) exhaustion ($M = 1.33$), 6 (22.2%) headache ($M = 1.26$), 2 (7.3%) others ($M = 1.19$) and no one reported sickness.

Error rate

Learning effects

Session as a fixed effect led to a significantly better model than the random intercept-only model, $\chi^2(3) = 85.97$, $p < 0.001$, $R^2 = 0.55$. As illustrated in Fig. 3, post hoc tests revealed a significantly lower error rate at T1 compared to

T0 ($\beta = -0.51$, SE = 0.08, $z = 6.83$, $p < 0.001$) and at T2 compared to T0 ($\beta = -0.66$, SE = 0.08, $z = 8.54$, $p < 0.001$). T1 and T2 did not differ ($\beta = -0.14$, SE = 0.08, $z = 1.86$, $p = 0.151$).

tDCS effects

Stimulation (sham vs. verum) did not have an effect on the error rate, $\chi^2(2) = 5.92$, $p = 0.052$, $R^2 = 0.56$ (see Fig. 4). Intensity as a fixed effect led to a significantly better model $\chi^2(2) = 6.83$, $p = 0.033$, $R^2 = 0.56$, but post hoc tests did not reveal a significant difference between 1 mA vs. 2 mA ($\beta = 0.93$, SE = 0.77, $z = 1.20$, $p = 0.231$). Also, within each intensity condition, no significant contrast between sham and verum stimulation emerged ($p > 0.05$).

Latencies of correct antisaccades

Learning effects

Session as a fixed effect led to a significantly better model, $\chi^2(3) = 168.14$, $p < 0.001$, $R^2 = 0.60$ (see Fig. 5). Post hoc tests reveal faster latencies of correct antisaccades at T1 vs. T0 ($\beta = 9.78$ ms, SE = 1.88, $z = 5.20$, $p < 0.001$), at T2 vs. T0 ($\beta = 19.25$ ms, SE = 1.85, $z = 10.39$, $p < 0.001$) and at T2 vs. T1 ($\beta = 9.48$ ms, SE = 1.83, $z = 5.16$, $p < 0.001$).

tDCS effects

The interaction between the fixed effect of stimulation and intensity led to the best model, $\chi^2(1) = 37.50$, $p < 0.001$, $R^2 = 0.49$ (Fig. 6). At the 1 mA condition, post hoc tests revealed significantly slower latencies of correct antisaccades under verum stimulation than sham stimulation

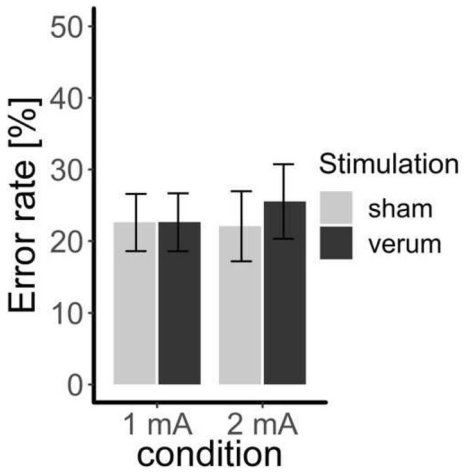

Fig. 4 The error rate (mean, standard error) depending on condition (1 mA vs. 2 mA) and stimulation (verum vs. sham) * $p < .05$

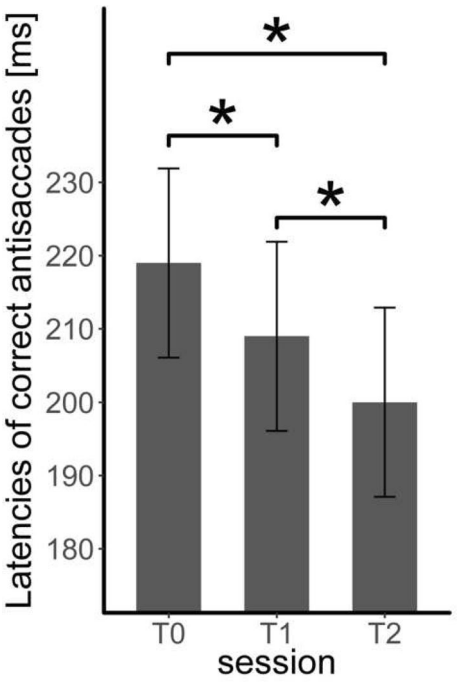

Fig. 5 The latencies of correct antisaccades (mean, standard error) at each study appointment (T0, T1 and T2) * $p < .05$

($\beta = -10.70$ ms, SE = 2.27, $z = -4.71$, $p < 0.001$, $d = 0.22$). With 2 mA stimulation, latencies of correct antisaccades were significantly faster under verum stimulation than sham stimulation ($\beta = 11.29$ ms, SE = 2.77, $z = 4.08$, $p < 0.001$, $d = 0.23$).

Change of binge eating episodes

The interaction between the fixed effect of session and intensity (Fig. 7) led to the best model ($\chi^2(2) = 10.89$, $p = 0.004$, $R^2 = 0.23$). The frequency of binge eating episodes decreased at the 2 mA condition ($\beta = 2.46$, SE = 0.69, $z = 3.56$, $p = 0.009$, $d = 1.56$), representing a strong effect, whereas it did not change significantly at the 1 mA condition ($\beta = -0.33$, SE = 0.60, $z = -0.56$, $p = 0.993$, $d = 0.21$).

Correlational analyses

A significant positive correlation was found between the BIS-15 total score and the error rate ($r_s = 0.60$, $S = 1182.10$, $p = 0.001$), whereas no significant correlation was found with the latencies of correct antisaccades ($r_s = 0.34$, $S = 1727.60$, $p = 0.101$). A significant positive correlation was found between the UPPS urgency scale and the latencies of correct antisaccades ($r_s = 0.46$, $S = 1391.80$, $p = 0.019$), whereas no significant correlation was found with the error rate ($r_s = 0.36$, $S = 2106.80$, $p = 0.068$). The other UPPS

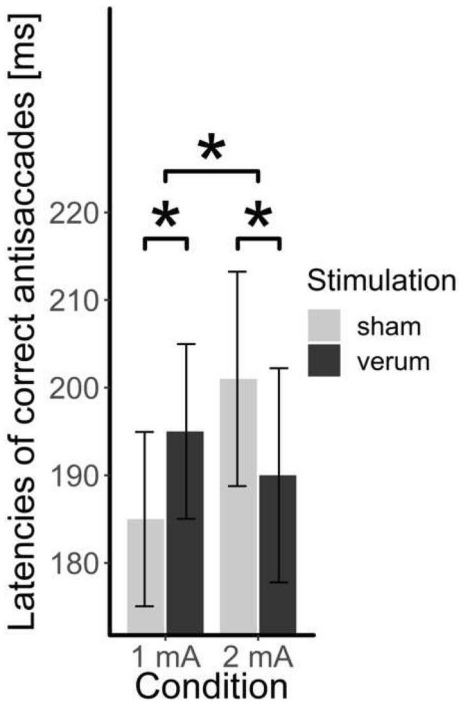

Fig. 6 The latencies of correct antisaccades (mean, standard error) depending on condition (1 mA vs. 2 mA) and stimulation (verum vs. sham) * $p < .05$

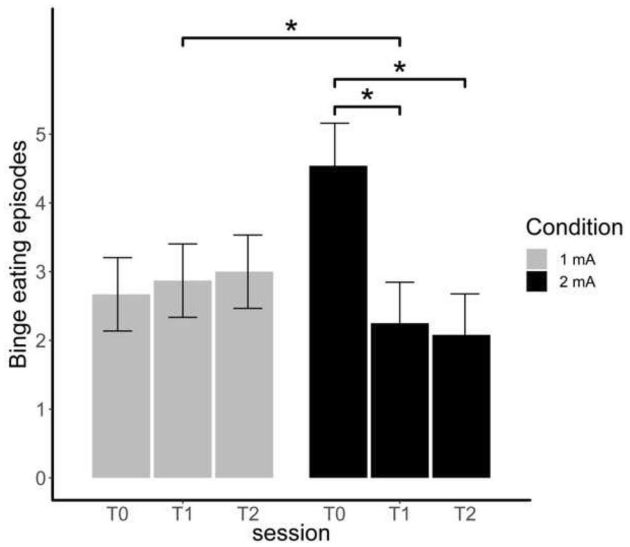

Fig. 7 Self-reported frequency of binge eating episodes in the last 7 days (mean, standard error) depending on condition (1 mA vs. 2 mA) and session (T0, T1 and T2) * $p < .05$

subscales and the TFEQ subscales did not correlate significantly with the eye tracking variables.

Discussion

In this double-blind, randomised, placebo-controlled proof of concept study, we investigated learning effects on a food-modified antisaccade task addressing response inhibition, and the effects of anodal 1 mA and 2 mA tDCS to the right dlPFC in a sample with BED. Overall, we could show improved response inhibition towards food stimuli as well as reduced binge eating frequency over time in the 2 mA condition. In line with our hypothesis about learning effects, patients improved over the three measurement points concerning error rate and latencies of correct antisaccades. Concerning our hypothesis about tDCS effects, the stimulation did not affect error rates, but the group that received 2 mA stimulation improved with faster latencies of correct antisaccades compared to sham stimulation, whereas the group that received 1 mA stimulation showed slower latencies. Moreover, only in the group that received 2 mA, a significant decrease of self-reported binge eating episodes over time could be observed, whereas no change was evident in the group that received 1 mA. Last, few, but strong positive associations between self-reported trait impulsivity with the performance in the food-modified antisaccade task could be found, i.e. BIS-15 was associated with an increased error rate and urgency correlated with longer latencies of correct antisaccades.

In more detail, a clear learning effect in the food-modified antisaccade task throughout the three measurement points could be observed. The error rate and the latencies of correct antisaccades decreased, indicating ameliorated response inhibition and goal-directed behaviour within three sessions. This is in line with previous training studies, where the error rates also decreased throughout the training [14]. This strengthens the assumption that underlying cognitive impairments in patients with BED can be modified by a repeated execution of a disorder-related task. Moreover, especially response inhibition tasks seem to be a useful basis for computer-assisted training programs in BED.

Concerning tDCS, no effect on the error rate of antisaccades could be observed. This is consistent with the notion that tDCS mainly influences the reaction times, not the accuracy of a response [50]. Accordingly, we observed faster latencies of correct antisaccades in the 2 mA condition which indicates that with this stimulation intensity, less effort is needed to execute the task. In other cognitive domains, it could already be demonstrated that a higher intensity is not inevitably accompanied by a better performance [29, 51], but in the current study, a lower intensity of tDCS (1 mA) even led to a worse performance. In the domain of BED, the positive effect of 2 mA tDCS is concordant with the study of Burgess et al. [26] who demonstrated enhanced cognitive control in patients with BED after 2 mA tDCS using bipolar

montage. Even if Burgess et al. [26] applied anodal stimulation to the right dlPFC simultaneously to cathodal stimulation to the left dlPFC which potentially impacts behaviour differently, a central role of the right dlPFC in BED can be assumed. The effect of 2 mA tDCS on the latency of correct antisaccades supports the idea of compensating the hypoactivated right dlPFC in patients with BED while doing the antisaccade task that demands response inhibition in a great extent. This provides support for the idea that underlying neural networks in response inhibition are altered in patients with BED and that this biopsychological marker can be targeted by tDCS. By application of 2 mA tDCS, the cortical excitability of the right dlPFC can be increased and, therefore, a significant improvement of response inhibition can be achieved. The possibility to modulate hypoactivated neural networks by 2 mA tDCS offers new options in multimodal treatment of BED.

Going beyond the experimental outcomes, a significant reduction of self-reported binge eating episodes over the measurement points emerged in the 2 mA condition contrary to the 1 mA condition. It is puzzling that the strongest decrease of binge eating episodes happened from T0 to T1 as we did not administer tDCS at T0. It could be that the learning effect from the food-modified antisaccade task on response inhibition was transferred to the psychopathology of patients with BED in everyday life. But in this case, we would expect ameliorations in both, the 1 mA and 2 mA condition. Another interpretation might be that this effect was due to the participation in the study itself, but this does also not explain why we found this effect only in the 2 mA and not in the 1 mA condition. In another pilot study from Giel et al. [14], binge eating frequency was also reduced after the antisaccade training, though the control group reduced binge eating frequency as well. Shafran et al. [52] could show in patients with eating disorders that decreased eating disorder pathology after CBT was accompanied by a decreased attentional bias in a laboratory task. Thus, although there is only limited and preliminary evidence, our results and the results from the two other studies might indicate that there could be a direct link between neurocognitive impairments like response inhibition and psychopathology like binge eating in BED. Thus, a coupling of non-invasive brain stimulation with a response inhibition training might be efficacious to reduce clinical outcomes as well.

One strength of this pilot study is that we assessed a representative sample of patients with BED who showed increased feelings of hunger and disinhibition while eating (TFEQ) compared with the general population [53]. This is in line with our theoretical model of increased impulsive eating behaviour in BED [6]. Concerning methodological aspects, to our knowledge, this is the first study combining neuromodulation techniques simultaneously with a behavioural task, where to date only one study concerning patients with BED is still ongoing [54]. The study was feasible and highly accepted, as the blinding worked, the participants complied with the 4-h fast, they reported only slight adverse events which are already well known and no one terminated the study due to discomfort, thus supporting the usage of tDCS in BED patients.

Nonetheless, some limitations should be addressed. The sustainability of the learning effect beyond the three sessions couldn't be evaluated as there was no follow-up assessment scheduled. Such a follow-up may be investigated in a systematic training study. Eating disorder pathology and trait impulsivity were not increased in the sample which might be a result of the excluded patients with increased scores in the ADHD scales. However, the correlations between impulsivity self-reports and eye tracking outcomes indicate that facets of trait impulsivity have been operationalized with the food-modified version of the antisaccade task. Impaired response inhibition in people with BED may be generalised rather than food specific [19]. Another limitation concerning the blinding of the participants to the stimulation is that we did not ask how confident they were about the session in which they got verum or sham stimulation though it is known, that expectations of receiving tDCS can significantly impact tDCS outcomes [55]. However, in the present study, we observed a nonlinear tDCS effect where participants in the 1 mA condition even got worse under verum stimulation. This is unlikely for expectation effects. Moreover, we observed a 55% rate of right guesses which is at chance level and participants in the 1 mA and 2 mA condition did not differ from each other. Unfortunately, we had to exclude a few participants and a considerable proportion of trials from data analyses to keep data quality high. However, with at least 3400 trials in each analysis and a robust statistical approach which takes interindividual variation into account, we could still analyse a huge and representative dataset.

Conclusion

In sum, this pilot study was carried out to combine tDCS with the food-modified antisaccade task to directly target food-related response inhibition as an intersection of impulsivity and cognitive control. The results suggest the modifiability of cognitive and biopsychological mechanisms in patients with BED and indicate that such a training programme with 2 mA stimulation of the right dlPFC might be useful for patients with BED concerning response inhibition. Based on these results, we will take the next step and develop such a training programme and explore its efficacy concerning clinical outcomes in a randomized, placebo-controlled, double-blind clinical trial that might enhance current CBT and decrease symptomatology in BED.

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Author contributions Katrin Elisabeth Giel, Christian Plewnia, Kathrin Schag, and Stephan Zipfel contributed to the study conception and design. Material preparation, data collection, and analysis were performed by Sebastian Max with support from Kathrin Schag. The first draft of the manuscript was written by Sebastian Max and Kathrin Schag and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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Data availability Data can be obtained on request to the author.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval This study was performed in line with the principles of the Declaration of Helsinki. Approval was granted by the ethics committee of the Medical Faculty Tübingen, Germany (No 459/2016BO2).

Informed consent Informed consent was obtained from all individual participants included in the study.

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ORIGINAL ARTICLE

Mind the food: behavioural characteristics and imaging signatures of the specific handling of food objects

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Abstract

In our world with nearly omnipresent availability of attractive and palatable high-calorie food, the struggle against overweight and obesity is a major individual and public health challenge. Preference for unhealthy food and eating-related habits have a strong influence on health, suggesting that high-calorie food triggers fast and near-automatic reaching and grasping movements. Therefore, it is important to better understand the specific neural mechanisms that control the handling of food involving a coordinated interplay between sensoric, motoric, and cognitive subsystems. To this end, 30 healthy participants (Ø BMI: 22.86 kg/m^2; BMI range: 19–30 kg/m^2; 23 females) were instructed to collect one of two concurrently presented objects (food vs. office tools) by manual movement in virtual reality (VR) and on a touchscreen. Parallel to the task in VR, regional brain activity was measured by functional near-infrared spectroscopy (fNIRS). In the VR and on the touchscreen, stimulus recognition and selection were faster for food than for office tools. Yet, food was collected more slowly than office tools when measured in VR. On the background of increased brain activity in the right dorsolateral prefrontal cortex (dlPFC) during food trials, this suggests more behavioural control activity during handling foods. In sum, this study emphasizes the role of the right dlPFC in faster recognition and selection of food as part of a food-valuation network, more controlled handling of food in the VR which highlights the relevance of medium for modelling food-specific embodied cognitions.

Keywords Virtual reality · Touchscreen · dlPFC · Behavioural control · Food-valuation network

Introduction

Rapid recognition and efficient collection of food have been pivotal skills in the successful evolutionary struggle for survival of species (Kivell et al. 2016). However, in modern environments with omnipresent availability of attractive and palatable high-calorie food, this preferential and "hard-wired" handling of food now represents a critical new challenge representing a key component in the steady rise of overweight and obesity (Spence et al. 2016). Despite widespread knowledge about the detrimental effects of excessive eating and obesity, compelling food appears capable of overcoming the rational and deliberate decision-making. A key mechanism in this connection seems to be the subjectively high value of food (Hardman et al. 2020).

Dual-system models of eating behaviour propose that an impulsive system is modulated by a reflective cognitive control system which, in the best case, supports adaptive behaviour and healthy food choice (Friese et al. 2011). Cognitive control is associated with the dorsolateral prefrontal cortex (dlPFC) (Cole and Schneider 2007; Egner and Hirsch 2005;

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Fales et al. 2008; MacDonald et al. 2000). The dlPFC plays a crucial role in situations with conflicts where decisions have to be made or activated representations in the working memory have to be updated (Badre and Wagner 2004). Especially the right dlPFC is involved in tasks in which response inhibition is needed to overcome impulsive prepotent actions (Blasi et al. 2006; Figner et al. 2010; Garavan et al. 2002; Knoch and Fehr 2007; Simmonds et al. 2008). Furthermore, the dlPFC is responsible for executing goal-directed behaviour based on integrating neural information of other cortical areas. As part of a specific food-valuation system, hedonic values are pre-processed in the orbitofrontal cortex (OFC) and transmitted to the dlPFC which initiates specific behaviour (Camus et al. 2009; Petrides and Pandya 1999). Already the mere presence of food stimuli can lead to an activation of the orbitofrontal cortex (Killgore et al. 2003; Morris and Dolan 2001). Attentional processes and processes of cognitive control are physiologically challenged in healthy populations if highly rewarding stimuli like food are involved (Chami et al. 2019). In different psychological paradigms, it could be shown that food can lead to either slowed (Janssen et al. 2017; Johansson et al. 2005; Nijs et al. 2010a) or speeded reactions (Castellanos et al. 2009; Hou et al. 2011; Werthmann et al. 2015), depending on the task demands and paradigms.

More complex appetitive behaviour like grasping movements can be investigated in controlled environments by means of virtual reality (VR) in combination with motion tracking. Food stimuli seem to play a specific role in grasping: Schroeder et al. (2016) reported that 3D objects of food were collected faster than ball objects in stimulus-irrelevant colour-cued grasping, but not warding. Relatively fast, but simple approach movements to various stimuli can be measured on touchscreens (Meule et al. 2019). It is quite possible that early stages of grasping behaviour reveal different behavioural patterns and that later stages are calling for a combined approach of touch- and VR-based methodologies (Gladwin et al. 2014). A systematic examination of differential and concordant effects of the medium on food valuation and behavioural control in the manual interaction with food stimuli has not been done yet and this study should provide further insights in the impact of the methodologies concerning modelling food-related differences in valuation and behavioural control.

To follow-up on the study of Schroeder et al. (2016), we established a more naturalistic scenario to investigate neurobehavioural manual movement initiation and execution based on recognition and decision processes. To this end, we implemented a binary-choice–forced-choice paradigm in a VR- and in a 2D-touchscreen setup to investigate differences in the interaction with food stimuli in natural unimanual hand movements and their neurophysiological correlates. We expect to evoke a situation where on the one hand cognitive control is challenged by presenting distractor and target stimuli simultaneously next to each other and on the other hand the food-valuation network is activated during presentation of food items. If the food-valuation network is more involved in the processing of the subjectively high value of food, we hypothesize a faster movement initiation towards food objects (Castellanos et al. 2009; Hou et al. 2011; Nijs et al. 2008, 2010b; Werthmann et al. 2013). If the cognitive control network is more involved, this should result in slower handling of food objects to prevent impulsive choices. Since the processing of alluring food stimuli likely involves more resources of the food-valuation network as well as cognitive control, it should enhance activity in the dlPFC. Accordingly, the amount of this neural activity should correlate with the interindividual differences in manual grasping movement of food objects.

Methods

Participants

Healthy, right-handed and non-obese participants were recruited through announcements and mails to the distributor list of a German university. In total 33, volunteers were recruited. From those, two participants were excluded due to technical problems in performing the task (bad hand tracking); one participant was excluded due to mental comorbidities. In total, 30 healthy individuals (23 women, $M_{age} = 22.30$, $SD_{age} = 4.61$, $N_{BMI>25} = 8$) participated in the experiment. Exclusion criteria were: left handedness, current dieting, neurological and mental diseases according to self-report, vegetarian and vegan diet, current or lifetime eating disorders according to clinical interview as well as BMI above 30. For their participation, the participants received either 8 €/h or course credits. The study was approved by the ethics committee of the Medical Faculty Tübingen (829/2018BO2) and all participants gave informed consent.

Apparatus

Virtual reality (VR)

During the behavioural task, participants were seated in a comfortable chair and wore a head-mounted display (HMD) which allowed for continuous tracking of head rotation (Oculus Rift CV1; Oculus VR, Inc., Menlo Park, USA). The HMD consists of two screens, both with a resolution of 1080 × 1200 pixels. The inter-pupillary distance was adjusted for each participant individually. A near-infrared sensor (Leap Motion Inc., San Francisco, USA) tracked the trajectories of the participants' hand. These trajectories were streamed in real time into the stereoscopic

display so the participants could interact with virtual stimuli through actual movements of their hand, comparable to our previous setups (Lohmann et al. 2018; Schroeder et al. 2016). Stereoscopic presentation was controlled by Unity 3D (5.6.2f1) with a bundled version of OVRPlugin. The leap motion device was positioned on a small table in front of participants and allowed for object interactions with the dominant hand in an area of approximately 1600 cm^2 (effectively covering most of the grasping range of the participants). The 3D-stimuli originated from the asset-store of Unity (Unity Technologies, San Francisco, USA) or Blender-models (Blend Swap, LLC). To realize matching of shape and colour of the stimuli, the objects got rescaled and recoloured. The stimuli set consists of the variations originating from the subcategories (balls, food, office objects). Ledoux et al. (2013) could show that food stimuli in the VR are comparable to pictures of food and real-life food concerning triggering food craving. In total, 48 different stimuli were used. Stimuli were rated by the participants concerning valence, arousal, grasp to urge, aesthetics, subjective estimated size and comfort of grasping on a continuous scale ranging from 0 to 100. Overall, stimuli were comparable regarding several practical dimensions except consumption value, see Appendix A.

2D touchscreen

To operate on the 23-inch 2D touchscreen (iiyama ProLite T2336MSC) with a resolution of 1920 × 1080 pixels, the participants wore touchscreen gloves. The start position of the hand was marked by a hand symbol on the screen. The location of the hand symbol was in the bottom-mid of the touchscreen that was positioned in a landscape orientation. The distractor and target stimuli were presented in the top left and top right corner of the horizontally oriented display. The resolution of the stimuli was 150 × 150 pixels. Most of the stimuli originated from a public picture data base (Blechert et al. 2014), which were used in a previous experimental setup (Meule et al. 2019). To realize matched photorealistic stimuli for the VR stimuli, the rest of the photorealistic stimuli were downloaded from the internet. Ledoux et al. (2013) could show that food-pictures are comparable to real-life food concerning triggering food craving. Half of the stimuli consisted of screenshots of the VR stimuli, the other half of photorealistic stimuli. Stimuli were rated by the participants concerning valence, arousal, grasp to urge, aesthetics, subjective estimated size and comfort of grasping on a continuous scale ranging from 0 to 100. Overall, stimuli were comparable regarding several practical dimensions except consumption value, see Appendix B.

Functional near-infrared spectroscopy (fNIRS)

An ETG-4000 Continuous Wave Optical Topography System (Hitachi Medical Co., Japan) was used to measure relative oxygenated (O_2Hb) and deoxygenated (HHb) blood concentration as indicators for brain activity (Fallgatter et al. 2004). The sampling rate was 10 Hz. Two 3 × 3 probe-sets with 12 measurement channels each and an inter-optode distance of 30 mm were placed over the left and right prefrontal cortex after the HMD was mounted. According to the international 10–20-system, one probe-set was placed over F3 (channel #7) whereas the other probe-set was placed over F4 (channel #19; see Fig. 4) (Jasper 1958). Using this configuration, the NIRS channels were predominantly located over the left and right dorsolateral (Brodmann areas 9 and 46) and inferior frontal cortex (Brodmann areas 44 and 45), as extrapolated from reference points based on the Colin 27 template (Singh et al. 2005; Tsuzuki and Dan 2014; Tsuzuki et al. 2007).

Procedure

Participants were instructed to not eat at least 3 h before the experiment and were asked at the appointment if they actually didn't eat. All participants declared conformity with this instruction. The whole experiment was conducted in a single session lasting approximately 2 h and typically took place between 11.00–13.30 and 15.30–19.30. After assessing demographic data, the absence of a current and lifetime eating disorder was examined by the section H of the SCID-I (Wittchen et al. 1997). Thereafter, participants were weighed on a scale. Height was determined by self-report. Food craving assessed by the Food Craving Questionnaire–State (Meule et al. 2012) before and after the task in the VR and can be looked up in Appendix C.

Afterwards, participants were equipped with the HMD and the behavioural task in the VR started. The task started with practice trials to familiarize the participant with operating the system. Then the fNIRS probe-set was mounted on the participants' head above the HMD. To start a trial, the participants had to put the hand in a standardized position. The start position of the right hand was marked by seven red coloured spheres which turned green if the start position was right. Subsequently, a fixation cross was presented which had to be aligned with a crosshair of the HMD for a duration of one second. Due to this fixation the participants had a standardized start position for their head and their gaze. With a stimulus onset asynchrony of 400 ms, a target and a distractor stimulus were presented concurrently next to each other. The participants were instructed not to move their hand until the stimuli were presented, otherwise an error message was displayed. If the target stimulus was presented on the left table, the distractor stimulus was presented on

the right table and vice versa. The positions of target and distractor stimuli were counterbalanced within a block. Each block consisted of 32 trials. The trial was finished, when the target stimulus was grasped and placed inside the box. If the participants placed the target stimulus outside of the box, grasped the wrong stimulus or took longer than four seconds for the grasping, an error message was displayed and the next trial started. The distance between the start position and the target stimulus was around 40 cm. The whole behavioural task in the VR consisted of six blocks. Across participants, block order was counterbalanced and each participant was randomly assigned to a block order. After each block, there was a short self-paced break. The whole task took about 15 min. An exemplary trial is shown in Fig. 1. Afterwards, the behavioural task was conducted at the 2D touchscreen without fNIRS.

The participants were seated in front of the horizontal oriented touchscreen with an angle of approximately 15° relative to the tabletop. The 2D touchscreen task was analogous to the task in the VR with the identical block order as in the VR. At the start of each trial, the participant had to touch a hand icon on the display with five fingers. After 500 ms, a fixation cross was presented for 1 s and with a stimulus asynchrony of 400 ms, the target stimulus and distractor stimulus were presented concurrently on the left and right top corner of the display.

According to the block instruction which was given before each block, the participant had to collect the target stimuli and drag it into a 2D model of a box. Due to faster startup procedures of each trial and faster movements in general, the whole task at the touchscreen took only around 10 min. An exemplary trial is shown in Fig. 2.

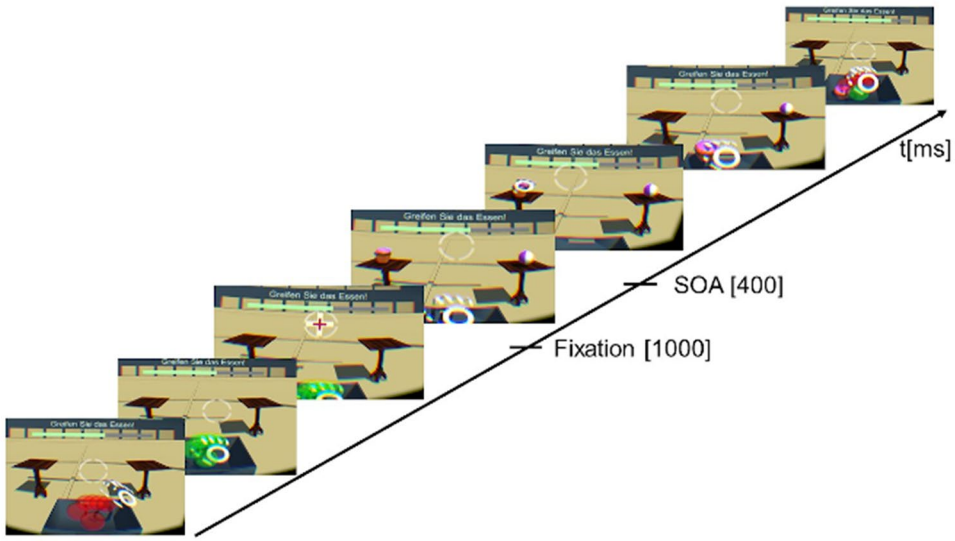

Fig. 1 An exemplary trial of the condition "food". The target stimulus which had to be grasped was a chocolate cupcake with pink icing. After the initial hand pose matches with the standardized hand pose, a fixation cross had to be aligned with the crosshair of the HMD for one second. With a stimulus asynchrony of 400 ms, the target and distractor stimulus were presented on the left and right table

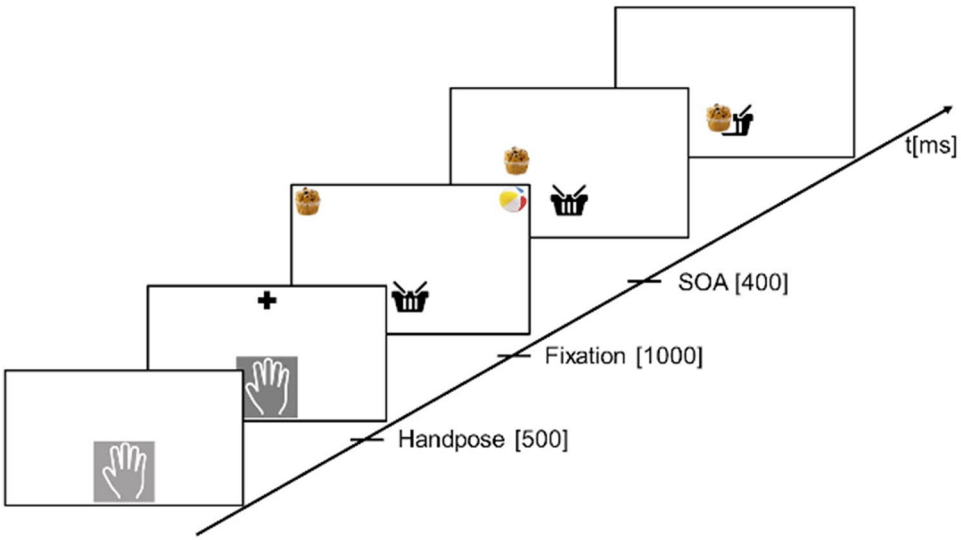

Fig. 2 An exemplary trial of the condition "food". The target stimulus which had to be grasped was a chocolate cupcake. After the hand icon has been touched with five fingers for 500 ms, a fixation cross was presented for one second. With a stimulus asynchrony of 400 ms the target and distractor stimulus were presented on the left and right top corner of the touchscreen

In both the VR task and the 2D-touchscreen task, each of the six blocks consisted of 32 trials. In two blocks each there were instructions to grasp different stimulus categories as fast and as correct as possible: food, balls or office tools. In each block, only two stimulus categories were presented. The order of the instruction was counterbalanced across all participants. Each stimulus category was twice selected as target and twice as distractor stimulus and paired with each other counterbalanced. Each variation of a stimulus category was presented randomized and balanced on the left and right table. Each pairing of the stimulus subcategories was realized.

Data analysis and statistics

Object rating analysis

All statistical inferences are conducted on a significance level of 5%. To estimate significance of valence of the different object categories (food, office tools, balls) paired *t* tests are conducted. Exploratory, to investigate the correlation between subjective food valence rating and reaction times, Pearson's correlation tests were conducted.

Behavioural data analysis

All statistical inferences are conducted on a significance level of 5%. Incorrect trials were excluded from all analyses (2.52%). Reaction times above 2000 ms and below 200 ms for the movement onset as well as reaction times above 4000 ms for the collection time on the touchscreen and in the VR were considered premature/incorrect. Movement onset is defined as the time between the presentation of the objects and the movement onset. Collection time is the time span after the participant's hand has left the start position until the participant's hand with the critical target has reached the position above the collection box where the target gets dragged into. Further, values deviating more than 2.5 SD, from individual cell means were considered outlier responses. 2.78 percent of the trials in the VR and 2.98 percent of the trials at the touchscreen were excluded. Only reaction times were analyzed as the block design is expected to affect reaction times rather than error rates (Zeligman and Zivotofsky 2017). To account for individual differences in motor grasping of grasp-affordant objects, we decided to standardize the reaction times for the food and office objects in relation to the ball objects. As grasping ball objects resembles exclusively motor actions which have to be executed fast and in an automatic manner, this seems to be a valid baseline correction. Furthermore, the ball objects are less complex than the other objects and demand less cognitive functions like planning. Each trial was subtracted by the individual's mean reaction time for ball objects. To measure effects of the different target stimuli on the manual grasping times in the VR compared to the touchscreen, the linear mixed model approach was used to account for individual differences in grasping food stimuli. All linear mixed models were calculated by the *lme4*-package of R (Bates et al. 2014). The linear mixed effect model approach contains a random effect for each subject which comprises the interindividual differences to the manipulated fixed effects, whereas the fixed effects are the averaged prediction of the fixed effects on the reaction times across all participants. To estimate the significance of each fixed effect log-likelihood tests between a linear mixed model with the fixed effect and a linear mixed model without the fixed effect were conducted. Two fixed effects were tested within the linear mixed model: the medium (VR vs. Touchscreen) and the category of the target stimuli (Food vs. Balls). Post hoc tests to test the different contrasts within a fixed effect of the linear mixed model, the *lsmeans*-package of R was used. This is based on the method of the least-squares means and post hoc tests are adjusted by Tukey method (Lenth 2016). To estimate the degrees of freedom of the post hoc tests, the Satterthwaite formula for degrees of freedom was used. Effect sizes for fixed effects were estimated by f^2 which can also be used in mixed linear models (Aiken et al. 1991; Lorah 2018).

An individual bias separately for movement onset and collection time for each participant was calculated by the difference of the ball-standardized reaction times of food objects and the ball-standardized reaction times of office tools:

$(RT_{Office} - RT_{Ball}) - (RT_{Food} - RT_{Ball})$. Therefore, a higher value indicates a more prominent shift towards food.

Further exploratory analysis with linear mixed models was carried out to investigate the impact of the valence differences of the two different objects that the participants faced during each trial on the reaction times towards food. For this, reaction times were aggregated across the participants. The difference score served as a fixed effect and a random intercept on each target stimulus was modelled.

fNIRS data analysis

Concentration changes of oxygenated (O2Hb) and deoxygenated haemoglobin (HHb) concentration were used for the fNIRS analysis, which was conducted using customized Matlab scripts (Matlab 2017a; The MathWorks, Inc., Natick, MA, USA). First, missing channels were interpolated before motion-based artefacts were corrected by the temporal derivative distribution repair (TDDR) method (Fishburn et al. 2019). To minimize further artefacts of non-neural causes, signal improvement relying on the assumption of a negative correlation between oxygenated and deoxygenated haemoglobin was conducted (Cui et al. 2010) during which the two signals were combined to one "true oxy signal"

which was then further analysed. A bandpass filter of 0.01 to 0.10 Hz was applied and around 3.60 percent of the channels with remaining artefacts were interpolated manually. A Gaussian kernel filter with a standard deviation of $\sigma = 40$ was then used to remove global physiological artefacts (e.g., related to respiration) (Zhang et al. 2016). Finally, the data were z-standardized and the mean z-transformed amplitude ranging from 10 to 40 s following the start of the block was individually exported for further statistical analysis [with a pre-task baseline of 5 s resting and separately for the individual average of both "food blocks" (food as target with distractor of balls or office tools), both "ball blocks" (ball as target with distractor of food or office tools) and both "office blocks" (office tools as target with distractor of food or ball)].

To be in line with previous statistical analysis, we decided to standardize the fNIRS BOLD response for the food and office objects in relation to the ball objects. The analysis focusses on the ball-object-corrected fNIRS BOLD signal between food and office objects. To measure effects of the different target stimuli on the fNIRS BOLD response, paired *t* tests between the conditions were performed and Bonferroni-corrected for multiple comparisons. Those paired *t* test were performed on the channels covering Brodmann area 9 (channel number (Ch) 8, 11, 13, 15, 16, 18, 20) and 46 (Ch 5, 9, 19, 21, 22) which both contribute to the dorsolateral prefrontal cortex (dlPFC), as well as Brodmann area 44 (Ch 6, 23) and 45 (Ch 2, 4, 7, 24) which both contribute to the inferior frontal gyrus (IFG).

Correlations between the fNIRS BOLD response and the individual biases of the manual actions were also calculated by Pearson's correlation test. An fNIRS BOLD response bias was calculated by the following formula:

$(\text{fNIRS-BOLD}_{\text{Food}} - \text{fNIRS-BOLD}_{\text{Ball}}) - (\text{fNIRS-BOLD}_{\text{Office}} - \text{fNIRS-BOLD}_{\text{Ball}})$. Therefore, a higher value indicates a higher shift towards food.

The individual behaviour biases for each participant were correlated with the individual fNIRS-BOLD response bias in the VR solely as there was no concurrent fNIRS measure at the touchscreen. Target areas of the fNIRS BOLD response were Brodmann area 9, 46, 44 and 45.

Results

Object ratings

In the VR, a significantly higher mean score concerning valence is reported for food items ($M_{VR} = 66.92$, $SD_{VR} = 14.68$) than for office tools ($M_{VR} = 51.29$, $SD_{VR} = 12.65$), $t(29) = 4.62$, $p < 0.001$, and for balls ($M_{VR} = 58.06$, $SD_{VR} = 10.97$). At the touchscreen, the mean valence of food items ($M_{TS} = 71.48$, $SD_{TS} = 13.74$) is significantly higher than for office tools ($M_{TS} = 51.15$, $SD_{TS} = 12.87$), $t(29) = 6.67$, $p < 0.001$, and significantly higher than for balls ($M_{TS} = 58.75$, $SD_{TS} = 13.66$), $t(29) = 4.78$, $p < 0.001$.

Effects of food on different stages of manual movement in VR and touchscreen

Movement onset

Including the category of target stimuli as a fixed effect in the mixed model leads to a significantly better model than the random intercept-only model, $\chi^2(1) = 106.87$, $p < 0.001$, $R^2 = 0.09$. The movement onset for the food objects as a target was significantly faster than for the office objects ($M = 19.04$ ms), $t = 10.38$, $SE = 1.84$, $p < 0.001$, $f^2 = 0.016$.

Including the medium as fixed effects in the mixed model leads to a significantly better model than the random intercept-only model, $\chi^2(1) = 355.49$, $p < 0.001$, $R^2 = 0.12$. The movement onset for the objects in the VR is significantly slower than at the touchscreen ($M = 34.43$ ms), $t = 19.18$, $SE = 1.80$, $p < 0.001$, $f^2 = 0.050$.

Including an interaction between the two fixed effects does not lead to a significantly better model, $\chi^2(1) = 1.49$, $p = 0.222$, $R^2 = 0.14$. This means the different levels of the fixed effects do not interact with each other. In Fig. 3a the ball-object-corrected reaction times of the movement onset are depicted. For the raw reaction times of the movement onset, see Appendix D.

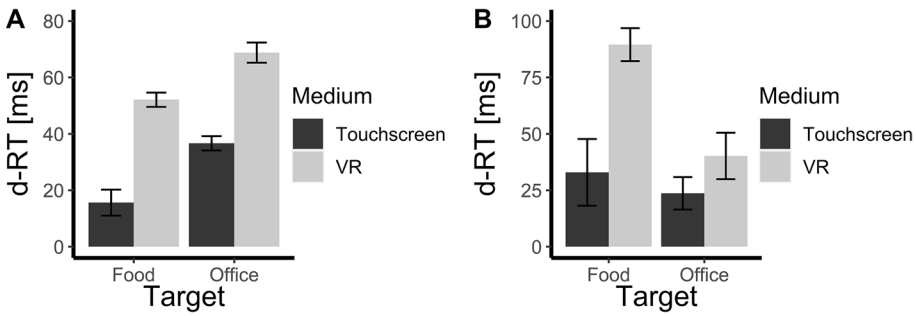

Fig. 3 Movement onset (**a**) and collection time (**b**) in relation to the movement onset reaction times of the ball objects. The bars represent the standard error of fixed effect estimates. d-RT were calculated by subtracting the reaction time of the target stimulus from the reaction time of the ball objects

Collection time

Including the category of target stimuli as fixed effects in the mixed model leads to a significantly better model than the random intercept-only model, $\chi^2(1) = 30.58$, $p < 0.001$, $R^2 = 0.11$. The same applies to the medium. This fixed effect in the mixed model leads to a significantly better model than the random intercept-only model, $\chi^2(1) = 49.27$, $p < 0.001$, $R^2 = 0.11$. Furthermore, those two fixed effects interact, $\chi^2(1) = 15.11$, $p < 0.001$, $R^2 = 0.12$. Whereas the collection time of food and office objects does not differ significantly at the touchscreen ($M = 9.31$ ms), $t = -1.29$, SE = 7.19, $p = 0.566$, the collection time of office objects is significantly faster than the collection time of food objects in the VR ($M = 49.34$ ms), $t = -6.70$, SE = 7.36, $p < 0.001$, $f^2 = 0.002$. That means, as soon as the participants have left their initial hand position, they collect office objects quicker than food objects, but only in the VR. In Fig. 3b the ball-object-corrected reaction times of the collection time are depicted. For the raw reaction times of the collection time, see Appendix D.

Object ratings and manual action in VR and at the touchscreen

In the VR, neither the movement onset time correlate with valence of food items ($r = 0.18$), $t(14) = 0.67$, $p = 0.512$, nor the collection time ($r = 0.22$), $t(14) = 0.86$, $p = 0.405$. At the touchscreen, neither the movement onset time correlates with valence of food items ($r = -0.11$), $t(14) = -0.42$, $p = 0.680$, nor the collection time ($r = 0.30$), $t(14) = 1.16$, $p = 0.266$.

For the movement onset in the VR, there is a significant impact of the difference of the valence between the two objects the participant faced during each trial on the movement onset ($\beta = -1.45$, $p < 0.001$). For each rating point difference concerning subjective valence between the two-faced objects, the movement onset for the food object got 1.45 ms faster. For the collection time in the VR, the difference of the valence is not a significant predictor ($\beta = 0.24$, $p < 0.816$). At the touchscreen, the difference of the valence does not predict the movement onset ($\beta = -0.56$, $p = 0.056$), nor the collection time ($\beta = -1.33$, $p = 0.146$).

Functional near-infrared spectroscopy (fNIRS)

Effects of stimuli categories on fNIRS BOLD response in VR

A strong prefrontal activation in the ball-standardized food condition in contrast to the ball-standardized office condition can be seen (Fig. 4). Especially in the region of the right dlPFC (Ch 19), a significantly higher activation in the food condition can be observed, $t(29) = 3.29$, $p = 0.047$. All other comparisons of the two standardized condition in other brain regions are not significant. All paired t tests conducted on the channels covering dlPFC and IFG are listed in Appendix E.

fNIRS BOLD response bias and manual movement in VR

A significant positive correlation ($r = 0.37$) between the fNIRS BOLD response bias of the right dlPFC and the movement onset bias is observed, $t(28) = 2.10$, $p = 0.044$. The stronger the fNIRS BOLD response to food objects in relation to office objects, the faster the decision to lift off the hand and to start approaching the food object compared to the office object. This correlation is depicted in Fig. 5. The correlation ($r = 0.13$) between the fNIRS BOLD response bias of the right dlPFC and the collection time bias is not significant, $t(28) = 0.71$, $p = 0.486$.

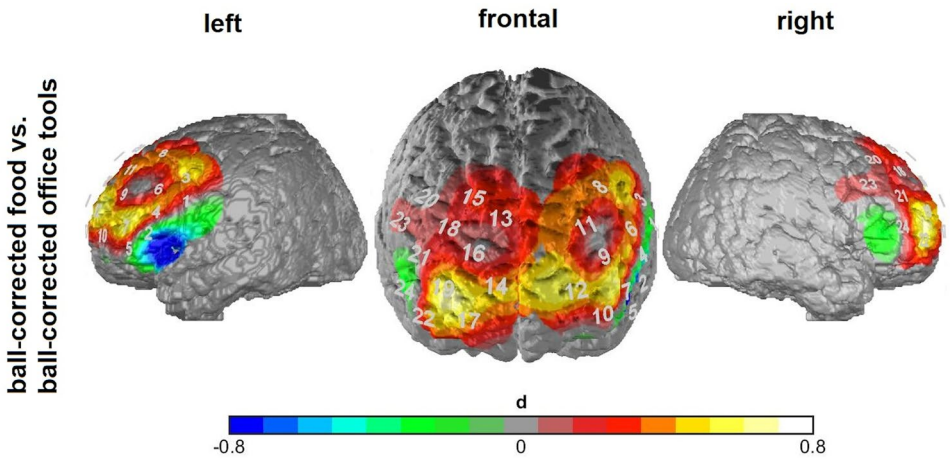

Fig. 4 Map for the functional near-infrared spectroscopy (fNIRS) data showing neural activity during the VR task. The numbers depicted resemble the corresponding channel numbers. The contrast between the ball-corrected food condition and the ball-corrected office condition is depicted and effect sizes are reported. Positive values indicate activation, negative values indicate deactivation

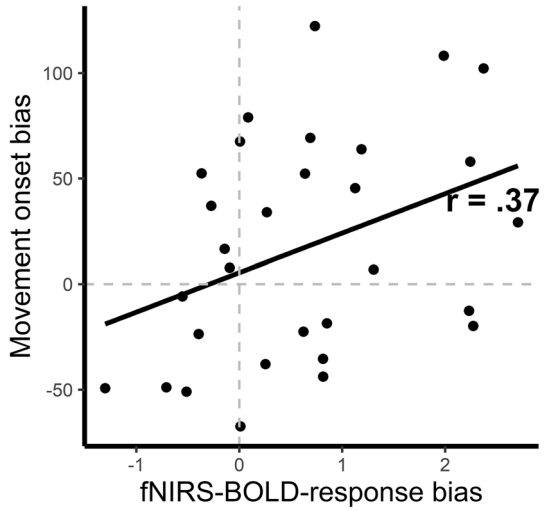

Fig. 5 Correlation between individual movement onset bias and fNIRS BOLD response bias in the right dlPFC in the VR. Movement onset bias was calculated by subtracting the ball-standardized reaction times for food objects from the standardized reaction times for office tools. A positive value indicates faster reaction times to food stimuli compared to office stimuli. fNIRS BOLD response bias was calculated by subtracting the ball-standardized z-transformed fNIRS BOLD response for office tools from the ball-standardized z-transformed fNIRS BOLD response for food objects. A positive value indicates more neural activity for food compared to office tools

Discussion

The present study revealed attentional and behavioural processes during the handling of food objects by assessing recognition and reaction times in both a VR setup and on a touchscreen device while further assessing fNIRS based brain activity during VR. We found that manual interaction with food stimuli goes along with enhanced neural activity in the right dlPFC. In line with our hypothesis concerning the involvement of a food-valuation network, we found a faster movement onset towards food as compared to office tools in both interfaces (VR and touchscreen) accompanied by higher neural activity in the right dlPFC. In line with our hypothesis concerning cognitive control, after movement initiation, a slower handling of food compared to office tools was observed in the VR. Of note, this effect was absent on the touchscreen.

A pivotal finding of this study is the enhanced neural activity in the right dlPFC when food stimuli were the target for the grasping movement. This food-related activity in the right dlPFC is in line with the proposal of the right dlPFC as a part of a specific food-valuation system (Camus et al. 2009). This model assumes an interconnection of the dlPFC and the orbitofrontal cortex (OFC) (Petrides and Pandya 1999). Hedonic values of stimuli are processed in the OFC and transmitted to the dlPFC to execute specific goal-dependent behaviour (Camus et al. 2009). Even if the participants are not free to choose which object they want to collect, an activation of a specific food-valuation system in the right dlPFC can be assumed since an adjustment of behaviour is required in each trial according to the localization of the food object. Apparently, food captures more neural resources in, for instance, estimating stimuli specific values and establishing goal-dependent behaviour. Therefore, it is reasonable to assume an additional food-specific effort.

The speeded reaction times of the first stage of manual interaction, the initiation of movement are in line with previous research. This stage involves the recognition and selection of two different object categories. Research using the visual dot probe paradigm showed elevated attentional processes towards food stimuli when compared to control stimuli (Castellanos et al. 2009; Hou et al. 2011; Nijs et al. 2008, 2010b; Werthmann et al. 2013). This could be due to the significantly higher value and survival relevance of food compared to office tools. Even if we did not find a significant correlation between valence of food objects and the reaction times, we could find a significant impact of the differences concerning subjective valence of the two concurrently presented stimuli. A higher difference in subjective valence led to faster movement initiation, thus highlighting the role of value in attentional selection and movement initiation processes involving food. On a neuropsychological level, those elevated attentional processes are associated with the right dlPFC, a brain region which is mostly known for its role in response inhibition (Blasi et al. 2006; Mostofsky and Simmonds 2008). The neuropsychological correlates of the current study highlight a more prominent role of the right dlPFC in selecting different target stimuli rather than suppressing an automatic response: the higher the brain activity in the right dlPFC, the faster the manual movement initiation. This correlational finding qualifies the role of the dlPFC in regulating early goal-directed behaviour in the interaction with food objects (Cornier et al. 2010; Horstmann et al. 2011).

The second stage of manual interaction, the collection time, was slower in food than in office tools and therefore is in line with the hypothesis of a cognitive control network. In contrast to the previous study by Schroeder et al. (2016) reporting a speeded collection time of food, we implemented a new paradigm to assess more naturalistic behaviour. In the current study, the participants had to react to a goal-relevant feature of this task and explicitly discriminate and select one out of two concurrently presented stimulus categories. Accordingly, a more conscious and controlled handling of food could indicate the higher hedonic value of food and its associated need to suppress an impulsive behaviour. As there was no significant correlation between the collection time and the brain activity in the right dlPFC, the involvement of the right dlPFC as a cognitive control network was not as prominent as part of a food-valuation network. Alternatively, attentional biases can be influenced by both appetitive and

aversive motivational processes (Field et al. 2016). The finding that differences in manual interaction with food were more prominent in the VR than at the touchscreen highlights the crucial role of response medium and the need for more methodological research. These differences in interaction with food stimuli provide information about its underlying mechanisms of food-valuation and cognitive control. It can be assumed that, particularly in the VR involving more complex and naturalistic behaviour and a higher level of immersion, a more careful and thus slower handling of food is a consequence of higher significance or personal importance of food objects. Consequently, VR seems more promising in possible future applications to modify specific behavioural biases, for example in eating disordered samples, whereas touchscreens potentially allow a wider and easier dissemination. While both media are able to reflect food-specific cognitive differences in the recognition-phase, VR seems to be more sensitive in modelling embodied cognition in the specific handling of food.

Conclusion

In sum, by means of a food-decision task in VR, we were able to document differences in interaction speed with food stimuli partially linked with higher activation in the right dlPFC. Faster movement initiation on the one side and slower handling of food on the other is consistent with the relatively higher appeal of food objects and a correspondingly more controlled interaction. These findings underline the significance of food valuation and cognitive control networks in manual interactions with food and the particular role of the right dorsolateral prefrontal cortex. Food-specific behaviour was more evident in the VR than at the two-dimensional touchscreen, which emphasizes the relevance of medium in modelling food-specific behavioural differences.

Investigating dynamics in a sample with disinhibited eating behaviour like obese subjects or patients with binge-eating-disorder could offer further insights in relevant behavioural characteristics and their neurophysiological signatures. These findings support the notion that targeted network stimulation and bias retraining may provide promising perspectives for an individualized modulation of disorders associated with an increased food bias. In this context, the use of immersive VR technology seems to be most promising for inducing behaviourally relevant effects.

Data availability statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Appendix A Ratings of VR stimuli

Stimulus	Mean valence (SD)	Mean arousal (SD)	Mean urge to grasp (SD)	Mean aesthetics (SD)	Mean subjective size (SD)	Mean grasp comfort (SD)
Baseball	57.69 (13.28)	42.89 (19.27)	47.41 (19.33)	52.13 (17.06)	42.57 (17.71)	64.87 (18.36)
Baseball_1	65.23 (14.98)	42.33 (26.15)	50.10 (22.72)	65.00 (18.46)	45.33 (18.12)	71.10 (22.79)
Baseball_2	48.20 (16.89)	47.10 (24.60)	44.30 (20.81)	40.73 (22.04)	42.13 (18.80)	61.57 (20.83)
Baseball_3	54.23 (16.93)	42.33 (22.20)	44.03 (23.88)	49.50 (20.86)	39.97 (18.98)	62.63 (21.15)
Baseball_4	63.10 (19.30)	39.80 (20.20)	51.20 (22.93)	53.27 (22.22)	42.83 (19.15)	64.17 (21.12)
Beachball	56.78 (14.14)	46.27 (17.79)	47.81 (18.22)	50.86 (18.08)	61.93 (13.35)	64.17 (15.93)
Beachball_1	60.60 (17.04)	51.13 (20.11)	49.80 (21.57)	55.47 (19.15)	61.17 (15.73)	62.83 (16.97)
Beachball_2	58.70 (15.92)	46.93 (20.31)	50.83 (18.20)	50.20 (22.11)	60.50 (13.71)	66.03 (17.48)
Beachball_3	53.57 (16.89)	44.33 (21.67)	45.13 (22.76)	48.83 (25.12)	63.10 (16.59)	62.40 (18.16)
Beachball_4	54.27 (16.42)	42.67 (21.77)	45.47 (20.02)	48.93 (19.63)	62.93 (14.15)	65.40 (19.61)
Handball	62.03 (17.77)	54.92 (19.61)	53.35 (18.77)	55.45 (19.87)	66.93 (14.82)	69.28 (17.54)
Handball_1	63.37 (22.40)	55.87 (23.69)	53.70 (25.03)	58.37 (26.62)	67.40 (15.09)	70.80 (18.89)
Handball_2	61.90 (23.67)	53.33 (26.67)	51.87 (22.85)	46.00 (28.60)	68.30 (15.53)	67.23 (22.99)
Handball_3	58.97 (20.93)	54.30 (20.76)	53.43 (21.96)	56.10 (27.08)	66.03 (15.31)	68.77 (15.84)
Handball_4	63.87 (18.45)	56.17 (22.92)	54.40 (19.18)	61.33 (20.16)	65.97 (16.62)	70.33 (17.46)
Tennisball	55.73 (11.17)	47.84 (18.35)	50.57 (18.08)	51.45 (17.15)	41.98 (19.82)	65.41 (16.00)
Tennisball_1	50.93 (15.80)	44.77 (20.02)	49.23 (23.54)	47.07 (22.98)	42.10 (20.72)	63.70 (20.52)
Tennisball_2	57.60 (14.45)	44.60 (20.71)	49.40 (17.34)	57.37 (21.48)	43.67 (21.40)	68.30 (18.26)
Tennisball_3	54.97 (17.94)	51.33 (21.96)	50.77 (21.15)	49.87 (21.90)	41.43 (20.82)	62.03 (22.33)

Stimulus	Mean valence (SD)	Mean arousal (SD)	Mean urge to grasp (SD)	Mean aesthetics (SD)	Mean subjective size (SD)	Mean grasp comfort (SD)
Tennisball_4	59.40 (19.05)	50.67 (22.50)	52.87 (22.98)	51.50 (26.60)	40.70 (19.13)	67.60 (16.91)
Burger	64.09 (18.16)	64.30 (17.66)	62.93 (19.35)	52.15 (20.19)	65.97 (11.49)	69.28 (17.64)
Burger_1	62.87 (21.15)	65.33 (21.28)	64.50 (21.22)	49.53 (25.27)	60.73 (13.21)	66.87 (19.43)
Burger_2	71.40 (20.99)	62.57 (20.50)	66.87 (21.17)	60.27 (22.72)	63.17 (14.73)	71.27 (20.43)
Burger_3	69.03 (22.17)	62.97 (23.42)	63.50 (23.63)	60.70 (24.83)	69.40 (14.67)	70.47 (17.80)
Burger_4	53.07 (24.53)	66.33 (22.15)	56.83 (25.41)	38.10 (24.45)	70.57 (14.75)	68.50 (20.28)
Cupcake	67.98 (15.99)	64.91 (16.48)	59.17 (20.22)	63.18 (16.81)	45.31 (16.01)	68.64 (16.88)
Cupcake_1	75.53 (15.33)	68.10 (19.21)	62.83 (25.73)	74.30 (16.28)	46.40 (19.12)	70.80 (19.80)
Cupcake_2	66.77 (15.63)	58.37 (22.02)	58.97 (22.61)	60.80 (20.63)	45.30 (15.87)	68.47 (15.86)
Cupcake_3	57.77 (25.15)	65.27 (19.43)	50.73 (22.78)	48.83 (26.95)	42.83 (16.52)	64.70 (21.57)
Cupcake_4	71.83 (19.34)	67.90 (17.69)	64.13 (23.40)	68.80 (20.46)	46.70 (18.40)	70.60 (17.17)
Donut	68.60 (17.71)	62.83 (20.90)	64.13 (23.40)	63.83 (16.53)	49.25 (12.85)	69.89 (15.20)
Donut_1	71.70 (16.83)	60.27 (22.88)	66.23 (22.05)	61.97 (19.27)	49.10 (13.01)	68.57 (21.36)
Donut_2	60.53 (20.99)	60.60 (24.08)	55.20 (24.84)	54.30 (24.87)	48.00 (14.41)	66.20 (17.07)
Donut_3	76.23 (19.57)	68.97 (23.91)	64.33 (24.23)	76.63 (17.42)	49.40 (18.00)	74.33 (16.33)
Donut_4	65.93 (22.85)	61.47 (21.94)	56.57 (24.57)	62.40 (21.57)	50.50 (16.90)	70.47 (17.73)
Pizza	67.01 (18.36)	61.01 (20.08)	60.40 (21.21)	53.87 (24.76)	71.08 (17.52)	47.11 (27.45)
Pizza_1	67.67 (21.28)	62.90 (23.19)	58.53 (26.45)	50.43 (27.97)	71.70 (17.73)	47.00 (28.57)
Pizza_2	69.53 (21.01)	61.37 (21.14)	62.23 (22.29)	58.77 (28.46)	71.47 (69.93)	45.97 (28.60)
Pizza_3	63.00 (22.14)	58.13 (25.70)	58.80 (23.20)	49.93 (28.51)	69.93 (18.20)	47.27 (28.94)
Pizza_4	67.83 (19.80)	61.63 (20.91)	62.03 (20.79)	56.33 (26.68)	71.23 (18.40)	48.20 (27.47)
Calculator	49.78 (19.22)	46.71 (16.77)	43.20 (20.42)	46.99 (18.73)	40.46 (15.65)	56.17 (20.46)
Calculator_1	51.00 (21.86)	43.77 (23.01)	42.70 (23.39)	47.87 (22.87)	39.60 (16.99)	53.67 (21.82)
Calculator_2	43.67 (25.11)	50.43 (24.36)	43.33 (27.67)	42.73 (29.42)	43.67 (17.71)	56.77 (25.59)
Calculator_3	53.30 (18.31)	49.97 (17.71)	47.13 (19.25)	54.73 (22.17)	40.03 (16.83)	57.13 (20.98)
Calculator _4	51.13 (20.98)	42.67 (18.17)	39.63 (20.71)	42.63 (22.49)	38.53 (15.56)	57.10 (20.31)
Folder	51.48 (15.01)	38.27 (17.50)	39.53 (18.53)	47.53 (14.20)	75.69 (18.77)	55.48 (21.05)
Folder_1	48.57 (20.60)	34.23 (22.61)	33.97 (19.31)	36.90 (24.46)	76.63 (20.12)	52.33 (24.49)
Folder_2	46.30 (23.75)	44.97 (24.27)	39.20 (24.98)	40.20 (27.17)	74.63 (19.04)	57.40 (24.11)
Folder_3	54.00 (16.41)	39.00 (20.20)	43.13 (18.48)	55.77 (16.80)	75.53 (18.36)	55.40 (22.34)
Folder_4	57.07 (19.22)	34.87 (21.20)	41.83 (24.37)	57.23 (21.28)	75.97 (20.10)	56.80 (20.48)
Hole-puncher	51.11 (14.33)	41.86 (16.33)	40.39 (16.65)	48.33 (17.78)	62.38 (16.09)	56.74 (21.64)
Hole-puncher_1	49.63 (17.67)	33.63 (20.80)	37.37 (19.20)	45.17 (22.26)	62.90 (18.62)	58.30 (22.60)
Hole-puncher_2	51.40 (22.06)	45.10 (22.39)	40.87 (22.08)	47.70 (27.99)	61.97 (16.83)	54.13 (26.10)
Hole_puncher_3	56.07 (20.78)	48.63 (20.27)	43.60 (19.94)	57.93 (24.77)	62.00 (15.95)	60.20 (22.36)
Hole_puncher_4	47.33 (17.09)	40.07 (17.83)	39.73 (15.83)	42.53 (21.90)	62.63 (16.96)	54.33 (23.65)
Stapler	52.80 (15.08)	41.16 (20.50)	40.78 (18.29)	52.03 (15.94)	40.38 (19.69)	56.08 (20.93)
Stapler_1	53.73 (15.79)	39.80 (20.58)	36.67 (20.32)	51.33 (20.67)	41.40 (21.72)	54.00 (22.37)
Stapler_2	53.50 (17.62)	42.57 (23.34)	42.57 (20.97)	53.47 (23.72)	40.20 (19.15)	55.20 (21.35)
Stapler_3	50.80 (20.56)	41.97 (24.34)	41.30 (21.62)	47.20 (26.38)	39.23 (19.46)	57.20 (24.33)
Stapler_4	53.17 (17.34)	40.30 (21.89)	42.60 (23.16)	56.10 (20.27)	40.70 (21.50)	57.90 (22.42)

Ratings on VR stimuli were reported on a visual analogue scale ranging from 0 to 100. 100 is reflecting a high score on the corresponding scale, whereas 0 is reflecting a low score. Mean ratings and standard deviations per category and per item are reported.

Appendix B Ratings of photorealistic stimuli

Stimulus	Mean valence (SD)	Mean arousal (SD)	Mean urge to grasp (SD)	Mean aesthetics (SD)	Mean subjective size (SD)	Mean grasp comfort (SD)
Baseball	58.87 (14.65)	50.87 (18.25)	44.03 (17.87)	53.25 (14.87)	47.87 (18.26)	62.85 (18.46)
Baseball_1	63.60 (16.19)	55.07 (18.41)	48.07 (16.88)	62.13 (20.69)	44.27 (16.43)	65.53 (17.30)
Baseball_2	56.67 (18.99)	51.33 (20.69)	42.27 (19.81)	44.33 (19.26)	51.73 (19.22)	61.73 (18.61)
Baseball_3	52.27 (16.52)	50.60 (20.53)	45.27 (19.56)	47.87 (21.71)	41.53 (18.59)	56.87 (20.72)
Baseball_4	62.93 (22.55)	46.47 (23.76)	40.53 (25.70)	58.67 (25.35)	53.93 (20.31)	67.27 (22.93)
Beachball	58.23 (15.06)	49.32 (20.64)	49.60 (18.99)	55.92 (17.68)	61.98 (16.04)	64.20 (16.73)
Beachball_1	56.27 (21.28)	41.67 (22.54)	48.80 (24.14)	51.93 (18.61)	67.47 (19.57)	63.87 (18.24)
Beachball_2	52.80 (15.62)	60.40 (20.85)	48.93 (20.91)	50.40 (24.18)	65.60 (16.76)	64.20 (20.13)
Beachball_3	67.87 (20.11)	53.73 (23.60)	56.20 (16.06)	67.80 (19.30)	55.13 (17.15)	66.00 (16.72)
Beachball_4	56.00 (8.47)	41.47 (19.32)	44.47 (20.35)	53.53 (13.78)	59.73 (12.90)	62.73 (16.41)
Handball	60.10 (20.43)	57.40 (18.68)	53.27 (22.49)	54.28 (22.03)	61.53 (15.38)	67.03 (16.85)
Handball_1	69.20 (20.95)	53.53 (21.81)	57.33 (25.74)	61.67 (24.67)	58.13 (15.97)	69.67 (15.59)
Handball_2	65.53 (25.28)	60.47 (23.35)	52.00 (28.40)	58.80 (27.49)	66.27 (15.53)	70.53 (20.79)
Handball_3	57.67 (21.28)	64.73 (14.00)	59.07 (18.83)	52.40 (24.96)	60.40 (17.72)	67.00 (17.16)
Handball_4	48.00 (15.31)	50.87 (16.24)	44.67 (17.81)	44.27 (15.55)	61.33 (14.19)	60.93 (15.98)
Tennisball	57.80 (18.41)	52.83 (20.19)	47.78 (21.00)	54.77 (19.82)	48.72 (18.38)	62.27 (18.72)
Tennisball_1	52.87 (16.59)	47.67 (24.25)	46.13 (19.95)	52.27 (18.63)	51.93 (14.86)	60.93 (16.15)
Tennisball_2	61.93 (16.10)	49.47 (23.33)	47.07 (18.18)	58.47 (15.94)	44.73 (17.42)	63.20 (20.44)
Tennisball_3	54.73 (20.79)	53.00 (22.89)	41.20 (22.07)	50.67 (22.60)	52.13 (20.14)	58.47 (20.33)
Tennisball_4	61.67 (23.88)	61.20 (20.91)	56.73 (25.73)	57.67 (31.25)	46.07 (21.67)	66.47 (23.15)
Burger	73.40 (15.05)	68.23 (17.15)	66.25 (21.90)	70.58 (17.16)	59.93 (14.24)	68.78 (15.98)
Burger_1	73.60 (13.03)	66.40 (20.63)	70.07 (16.88)	70.53 (19.11)	56.87 (11.88)	67.80 (11.68)
Burger_2	82.40 (13.45)	71.60 (18.50)	67.00 (24.52)	77.27 (18.09)	59.40 (14.09)	72.07 (14.96)
Burger_3	74.87 (15.02)	63.27 (16.78)	60.13 (23.84)	73.20 (11.27)	58.33 (15.97)	67.67 (16.11)
Burger_4	62.73 (25.06)	71.67 (20.81)	67.80 (25.76)	61.33 (25.47)	65.13 (19.30)	67.60 (25.67)
Cupcake	69.07 (16.04)	62.95 (19.46)	62.28 (21.20)	66.92 (19.40)	52.58 (16.08)	67.88 (16.11)
Cupcake_1	72.60 (14.50)	62.67 (21.29)	63.07 (18.97)	69.80 (22.05)	52.20 (20.27)	67.60 (17.39)
Cupcake_2	62.40 (24.48)	61.00 (18.67)	61.73 (22.36)	55.73 (24.66)	53.40 (17.88)	63.00 (19.73)
Cupcake_3	74.93 (13.83)	66.33 (17.59)	66.87 (23.56)	76.67 (19.63)	49.93 (13.31)	72.40 (14.33)
Cupcake_4	66.33 (18.36)	61.80 (24.79)	57.47 (26.23)	65.47 (20.71)	54.80 (15.17)	68.53 (16.41)
Donut	65.68 (18.18)	56.65 (19.61)	55.63 (23.05)	64.32 (21.39)	51.57 (17.11)	66.97 (16.42)
Donut_1	65.87 (18.63)	55.07 (17.40)	48.47 (22.05)	61.53 (19.20)	51.40 (20.00)	64.20 (20.41)
Donut_2	62.13 (25.13)	56.20 (22.40)	53.27 (25.28)	61.47 (23.25)	47.47 (18.69)	64.40 (17.53)
Donut_3	73.53 (16.22)	59.33 (21.96)	58.87 (26.99)	75.07 (17.13)	59.87 (18.60)	71.00 (17.62)
Donut_4	61.20 (23.58)	56.00 (25.63)	61.93 (20.76)	59.20 (32.09)	47.53 (15.15)	68.27 (15.49)
Pizza	77.78 (14.85)	70.45 (18.27)	67.92 (22.27)	76.18 (17.44)	64.12 (21.98)	72.78 (14.97)
Pizza_1	77.87 (12.56)	67.67 (18.82)	69.87 (18.76)	77.73 (19.96)	63.80 (23.82)	71.27 (15.40)
Pizza_2	79.13 (14.53)	72.80 (14.79)	71.87 (24.29)	84.20 (13.46)	62.53 (19.87)	75.33 (15.67)
Pizza_3	74.33 (17.27)	65.00 (21.23)	62.60 (19.69)	65.73 (24.07)	65.13 (22.51)	69.87 (15.40)
Pizza_4	79.80 (19.87)	76.33 (22.47)	67.33 (29.48)	77.07 (18.69)	65.00 (24.67)	74.67 (17.85)
Calculator	47.88 (18.81)	37.57 (22.12)	37.22 (20.75)	39.67 (17.38)	46.97 (15.61)	59.35 (21.25)
Calculator_1	44.67 (14.89)	25.40 (15.70)	28.93 (15.48)	31.53 (13.96)	40.87 (18.02)	56.20 (22.31)
Calculator_2	49.33 (23.74)	49.53 (22.68)	43.13 (21.98)	37.87 (26.01)	49.93 (18.34)	56.40 (17.19)
Calculator_3	45.47 (16.23)	40.00 (22.88)	36.40 (20.65)	40.13 (18.27)	44.13 (14.96)	61.33 (23.82)
Calculator _4	52.07 (22.74)	35.33 (27.82)	40.40 (25.94)	49.13 (18.10)	52.93 (18.99)	63.47 (26.37)
Folder	52.10 (15.35)	37.37 (22.31)	37.68 (20.27)	50.83 (16.76)	64.65 (21.46)	65.50 (19.77)
Folder_1	47.40 (19.57)	30.73 (29.16)	28.20 (21.01)	41.27 (20.12)	63.73 (23.28)	67.33 (20.87)

Stimulus	Mean valence (SD)	Mean arousal (SD)	Mean urge to grasp (SD)	Mean aesthetics (SD)	Mean subjective size (SD)	Mean grasp comfort (SD)
Folder_2	47.73 (18.66)	42.60 (25.96)	39.00 (25.28)	47.13 (27.15)	65.67 (23.12)	59.47 (24.75)
Folder_3	54.13 (13.75)	39.20 (22.59)	40.47 (24.72)	56.67 (11.51)	64.27 (23.79)	70.67 (18.83)
Folder_4	59.13 (16.75)	36.93 (20.58)	43.07 (15.70)	58.27 (18.87)	64.93 (19.20)	64.53 (17.71)
Hole-puncher	54.53 (14.24)	34.48 (21.13)	38.88 (15.81)	49.38 (17.11)	50.38 (14.92)	62.43 (17.67)
Hole-puncher_1	54.53 (13.38)	34.87 (27.19)	35.47 (20.12)	49.40 (24.35)	48.27 (17.16)	62.53 (20.63)
Hole-puncher_2	53.87 (20.06)	37.20 (22.28)	40.13 (21.75)	49.60 (21.37)	57.73 (16.88)	62.33 (20.65)
Hole_puncher_3	50.53 (19.19)	34.53 (20.42)	41.00 (14.29)	46.80 (16.35)	45.93 (14.39)	61.07 (14.84)
Hole_puncher_4	59.20 (13.63)	31.33 (22.48)	38.93 (17.60)	51.73 (18.02)	49.60 (12.98)	63.80 (19.21)
Stapler	50.08 (14.84)	36.68 (22.77)	37.53 (19.96)	44.12 (18.17)	46.12 (18.00)	63.68 (19.64)
Stapler_1	52.40 (14.81)	32.73 (25.27)	29.47 (19.63)	44.93 (17.66)	39.67 (15.89)	63.60 (20.65)
Stapler_2	51.33 (18.23)	32.33 (22.97)	40.93 (23.48)	47.07 (19.52)	52.87 (19.22)	69.67 (20.58)
Stapler_3	46.00 (17.01)	37.00 (25.88)	32.87 (18.57)	33.93 (26.34)	41.13 (14.99)	55.60 (21.41)
Stapler_4	50.60 (17.26)	44.67 (20.73)	46.87 (19.15)	50.53 (19.44)	50.80 (21.00)	65.87. (17.26)

Ratings on photorealistic stimuli were reported on a visual analogue scale ranging from 0 to 100. 100 is reflecting a high score on the corresponding scale, whereas 0 is reflecting a low score. Mean ratings and standard deviations per category and per item are reported

Appendix C FCQ-S before and after the behavioural task in the VR

Scale	Mean score pre (SD)	Mean score post (SD)	*t* test
Desire to eat/loss of control	13.23(4.04)	14.07(5.23)	$t(29) = 1.21$, $p = 0.236$
Positive affect	15.03(4.61)	15.93(5.66)	$t(29) = 1.72$, $p = 0.096$
Hunger	9.2(2.66)	10.20(2.61)	$t(29) = 3.94$, $p < 0.001$

The FCQ-S assesses the desire to eat a specific food as a state variable. 15 items subdivide into three subscales: intense desire to eat/loss of control (6 items), positive affect (6 items) and hunger (3 items). Each item scores from 1 ("strongly disagree") to 5 ("strongly agree"). Mean ratings and standard deviation for each scale are depicted. *t* Tests for dependent samples were performed to estimate pre-post-differences

Appendix D Reaction times without standardization

	Mean RT balls (SD)		Mean RT food (SD)		Mean RT office tools (SD)	
	VR	Touchscreen	VR	Touchscreen	VR	Touchscreen
Movement onset	521.92 (99.49)	455.05 (81.49)	574.33 (103.86)	470.69 (85.67)	590.89 (114.69)	491.09 (85.18)
Collection time	1049.01 (343.89)	766.82 (171.83)	1139.03 (397.71)	797.86 (180.39)	1089.68 (367.05)	790.21 (174.24)

The table depicts raw mean reaction times and standard deviations of the movement onset and collection time for each stimulus category (balls, food, office tools) dependent on the medium (VR, touchscreen)

Appendix E fNIRS-BOLD response of ball-standardized food- and office tool-condition

Brodmann area (BA)	L ch	t	p_{cor}	R ch	t	p_{cor}
Ball-standardized food vs. office tool condition						
BA 9	8	1.76	1	13	0.80	1
	11	1.12	1	15	1.14	1
				16	0.28	1
				18	0.61	1
				20	0.23	1
BA 44	6	1.29	1	23	0.37	1
BA 45	2	− 2.44	0.376	24	− 0.41	1
	4	1.24	1			
	7	2.59	0.268			
BA 46	5	− 1.05	1	19	3.29	0.047*
	9	0.48	1	21	0.66	1
				22	2.18	0.673

* Indicates $p < 0.05$. ** indicates $p < 0.01$. Reported p values were Bonferroni-corrected for multiple comparisons.

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ORIGINAL RESEARCH
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A Pilot Event-Related Potentials Study on Mechanisms Underlying a tDCS-Enhanced Food-Specific Response Inhibition Task for Patients With Binge Eating Disorder

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Behavioural studies demonstrate alterations in cognitive functioning, particularly impaired response inhibition and increased attentional bias towards food in binge eating disorder (BED). This pilot study aimed to investigate the neurophysiological processing of a food-specific inhibition training combined with anodal transcranial direct current stimulation (tDCS) of the right dorsolateral prefrontal cortex (DLPFC) in 16 patients with BED (mean age = 38.6, mean BMI = 33.7 kg/m^2). Patients performed a food-specific antisaccade task at baseline (T0) and in a cross-over design with verum vs. sham stimulation at T1 and T2. We investigated (i) event-related potentials (ERPs; N2, ERN and P3 amplitudes) while executing the task at baseline, (ii) whether baseline ERPs would predict task performance at T1 and T2 and (iii) associations between ERPs, eating disorder pathology and impulsivity at baseline. The mean amplitude of N2 was less pronounced in erroneous saccades (ES) than correct saccades (CS), whereas ERN and P3 mean amplitudes were more pronounced in ES. Moreover, the P3 mean amplitude of ES predicted the percentage of ES at both follow up-measurements irrespective of the applied stimulation (sham vs. verum). N2 in trials with correct saccades were negatively correlated with nonplanning trait impulsivity, while P3 in erroneous antisaccade trials was negatively correlated with food-related impulsivity. Overall, the findings of reduced ERN, enhanced P3 and N2 amplitude might be interpreted as difficulties in response inhibition towards food in individuals with BED. In particular, P3 predicts task outcome at follow-up and might represent a potential marker for inhibitory control processes.

Keywords: binge eating disorder, response inhibition, impulsivity, antisaccade, cognitive control, event-related potentials

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INTRODUCTION

As the most recent eating disorder (ED) diagnostic category in the Fifth Edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5; American Psychiatric Association, 2013), binge eating disorder (BED) is characterised by recurrent binge eating episodes in which a person consumes a large amount of food in a discrete period of time. These episodes of binge eating are further accompanied by a sense of loss of control. BED is the most common ED with a prevalence ranging between 1–4%. Patients with BED have been further found to suffer from a high rate of both mental and somatic comorbidities (Kessler et al., 2013; Keski-Rahkonen and Mustelin, 2016).

Problems in cognitive functioning have been suggested to be core underpinnings for the development and maintenance of BED. Several reviews have demonstrated impaired response inhibition, executive planning, decision making, cognitive flexibility, as well as increased attentional biases and reward sensitivity to food related stimuli among individuals with BED (Kittel et al., 2015; Kessler et al., 2016; Giel et al., 2017b; Stojek et al., 2018). These concepts are all related to the personality trait impulsivity (Dawe and Loxton, 2004; Gullo et al., 2014; Sharma et al., 2014), and among patients with BED this is expressed through impulsive food-related behaviours (Giel et al., 2017b).

Regarding cognitive functions, several inhibitory control tasks (e.g., antisaccade task, Go/No-Go tasks, and Stop Signal task) have been designed to test an individual's ability to stop, change or delay impulsive behavioural responses associated with highly rewarding cues. For instance, in the food-specific antisaccade task which is also administered in this study, participants are asked to look in the opposite direction of the stimulus as quickly as possible when a food-related stimulus appears on the computer screen (Giel et al., 2017a). In such inhibitory control tasks, individiuals with BED experience greater difficulty in suppressing the dominant response, thus demonstrating deficits in inhibitory control towards food stimuli (Hege et al., 2015; Preuss et al., 2019).

In addition to behavioural investigations, event-related potentials (ERPs) derived from electroencephalography (EEG) recordings that measure cortical activity with a high temporal resolution have been used to investigate food-related cognitive processes including response inhibition (Svaldi et al., 2010; Luck, 2014; Leehr et al., 2018; Chami et al., 2019). While making a decision about which ERP components need to be used, characteristics of the stimuli (e.g., sensory, auditory, visual) and targeted cognitive processes are taken into consideration (Luck, 2014). Especially, the inhibitory control related components N2 (observed around 200–300 ms after stimulus presentation), P3 (observed around 300–600 ms after stimulus presentation) and error-related brain potentials (ERN; observed around 50–150 ms after erroneous behaviour) appear to be of particular interest in response inhibition studies. Therefore, for the scope of the current study, we are focusing on N2, P3 and ERN components. The N2 component is a negative deflection that is associated with inhibitory control, conflict monitoring, and automatic response tendencies (Falkenstein, 2006; Leehr et al., 2018; İceta et al., 2020). Particularly N2b (300–360 ms) plays an important role in the attentional detection of deviation from perceptual novelty or deviation from a dominant visual stimulus (Kopp et al., 1996; Folstein and Van Petten, 2008). During the antisaccade task, it is expected that N2 amplitude should be more pronounced, when behaviour is inhibited (correct saccades), in comparison to disinhibited behaviour (erroneous saccades). Another core psychophysiological component that is associated with error processing is the error negativity (Ne; Falkenstein et al., 1991) also known as the error related negativity (ERN; Gehring et al., 1993). ERN/Ne is a sharp negative-going deflection that can be detected after both conscious and unconscious errors (Nieuwenhuis et al., 2001). During the antisaccade task, it is expected that ERN amplitude should be more pronounced during disinhibited behaviour (erroneous saccades), in comparison to inhibited behaviour (correct saccades). The P3 component is a positive deflection that is associated with various functions such as attention, memory, motivation and response inhibition. P3a is generally enhanced within frontocentral electrodes and shown to be relevant to tasks involving inhibition of an overt response (Dimoska et al., 2006; Gajewski and Falkenstein, 2013). Meanwhile, P3b is more enhanced within parietal electrodes and has been shown to be relevant in motivating attention (Chami et al., 2019). More specifically, it is associated with attentional biases towards food given its rewarding nature across different weight and age groups (Nijs et al., 2008; Hill et al., 2013; Hofmann et al., 2015; Biehl et al., 2020; İceta et al., 2020). During the antisaccade task, it is expected that P3 amplitude should be increased during behaviour inhibition (correct saccades) due to increased inhibitory control, or else during behaviour disinhibition (erroneous saccades) due to the attention-grabbing properties of food.

While an extensive number of studies have investigated ERPs related to inhibitory control mechanisms, cross-sectional ERPs studies on response inhibition towards food are limited with heterogeneous findings. One such study by Leehr et al. (2018) examined inhibitory control with a food-related antisaccade task under negative mood conditions in individuals with BED using a combination of eye tracking (ET) and EEG. The authors found significantly larger N2 latencies in overweight individuals without BED than in overweight individuals with BED. ERN/Ne amplitudes were increased for erroneous saccades in comparison to correct saccades regardless of weight or BED status. Meanwhile, through use of the auditory oddball paradigm, İceta et al. (2020) recently found that participants with obesity showed a reduction in P3 and N2 amplitude compared to normal-weight participants, regardless of food disinhibition problems. The authors found that especially the N2 amplitude was associated with clinical markers (i.e., higher self-reported drive for thinness and binge eating), within this group of participants. Another ERP study conducted with a sample of adolescents showed that only those participants with healthy weight had significantly higher P3 amplitudes towards high-calorie food, as opposed to low-calorie food or neutral items. These effects were not found among participants with overweight/obesity (Biehl et al., 2020).

Throughout the literature, it has been emphasised that the inhibition skills and psychopathology of individuals with BED

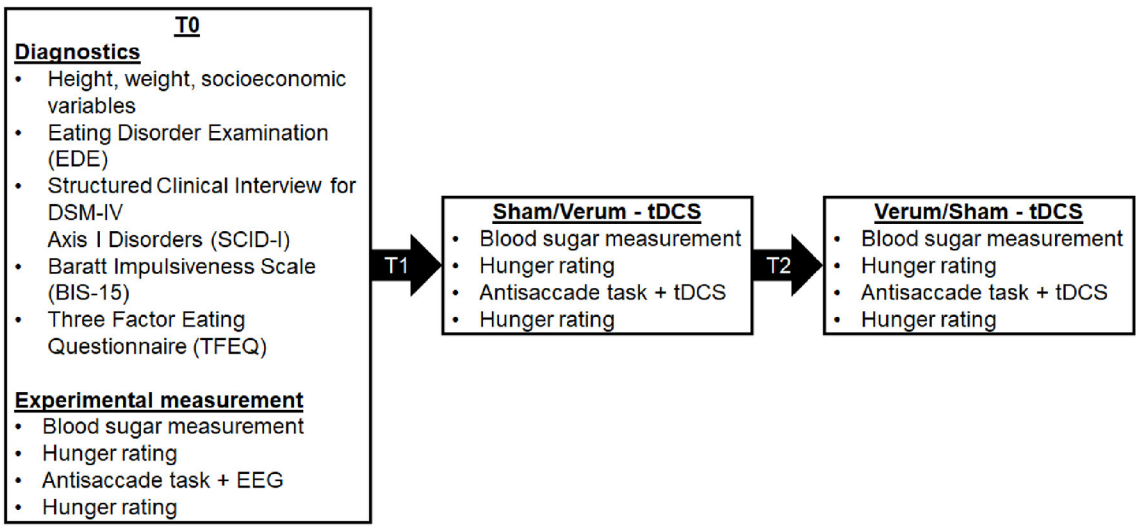

FIGURE 1 | An overview of the study appointments (T0, T1, T2) and the assessed data. The allocation to the two stimulation conditions (verum and sham stimulation) was randomised, counterbalanced and double-blind.

may show improvement following interventions and training programs targeting food-related impulsivity (Giel et al., 2017a; Brockmeyer et al., 2019; İnce et al., 2021). For example, a recent pilot trial of our workgroup was conducted to test the efficacy of a food-modified antisaccade task combined with transcranial direct current stimulation (tDCS) to improve response inhibition in patients with BED (Max et al., 2021). Patients underwent anodal verum and sham tDCS stimulation of the right dorsolateral prefrontal cortex (dlPFC) in a crossover placebo-controlled design. Within three sessions, the error rate and latencies of correct saccades were decreased, indicating improved response inhibition. Although no effect was found regarding the error rate of antisaccades following tDCS administration, receiving 2 milliampere (mA; an indicator of electrical current intensity) stimulation could significantly reduce the latencies of correct saccades compared to sham stimulation. Thus, a response inhibition training for patients with BED seems fruitful. However, it remains unknown whether underlying neurocortical mechanisms related to response inhibition towards food would change as well. To investigate this effect, Lapenta et al. (2014) aimed to reduce food craving in healthy females through increased inhibitory control with tDCS of the dlPFC. In a subsequent Go/No-go task, decreased N2 negativity and significant increase in P3 positivity were found for No-go stimuli following active tDCS. Another study examined the behavioural and ERPs changes following a food-specific Go/No-go task as inhibitory control training in patients with BN and BED in comparison to a control training (Chami et al., 2020). Neither of these interventions significantly changed the N2 or P3 amplitudes from baseline to post-intervention. These heterogenous findings imply that food-specific inhibition trainings might not change ERPs (Chami et al., 2020), but that tDCS could have an effect on ERPs (Lapenta et al., 2014). In the current pilot study, we aim to gain a more in-depth understanding of the potentially underlying neuropsychological mechanisms of inhibitory control in patients with BED. Through this specialised focus on neurophysiological mechanisms, we investigate the EEG activity of a subgroup of patients with BED previously assessed during a study by Max et al. (2021). More specifically, we investigate the following hypotheses:

I. During the food-modified antisaccade task in patients with BED at baseline (T0), there will be differences between erroneous vs. correct saccades for the mean amplitudes of ERPs. In details, we expect the N2 amplitude to be less pronounced in erroneous vs. correct saccades due to decreased response inhibition. Meanwhile, we expect the ERN amplitude to be more pronounced in erroneous vs. correct saccades. Concerning P3 amplitude, we expect that erroneous than correct saccades differ as well, though based on the evidence cited above, the direction is unclear.
II. The three ERP mean amplitudes (N2, ERN, P3) will be associated with the task performance and they will predict behavioural task performance during the T1 and T2 study appointments with verum vs. sham stimulation.
III. The three ERP mean amplitudes (N2, ERN, P3) will be associated with clinical markers at baseline, e.g., eating pathology, trait impulsivity and food-related impulsivity.

METHODS

Study Design

An overview of the study design can be seen in **Figure 1**. In summary, we completed EEG assessments during baseline measurement (T0) while patients completed the food-modified antisaccade task. We repeated the antisaccade task while patients received tDCS stimulation (verum vs. sham) in a cross-over design at T1 and T2. In the pilot study from Max et al.

(2021), we additionally investigated the influence of tDCS and cognitive training on inhibitory control with different stimulation intensities (1 mA vs. 2 mA), however, this is not the focus of the current study.

Participants

Patients in the current study were a subgroup of the sample recruited by Max et al. (2021). All patients were right-handed adults (age range 20–63) with a diagnosis of BED. Patients with normal weight or overweight/obesity (BMI > 18.5 kg/m^2) were included. Exclusion criteria included a diagnosis of attention deficit hyperactivity disorder (ADHD), psychotic disorders, bipolar-I disorder, current alcohol or drug addiction, current suicidality, current pregnancy, current physical illnesses which influence weight or eating behaviour, unstable medication (changed medication within the past two weeks), neurological diseases, current prescription of neuroleptics or benzodiazepines, current attendance to structured dieting programs, past bariatric operations, metallic implants in the head and eye diseases.

From a sample of 60 initially interested individuals in the whole project (Max et al., 2021), nine declined interest and 20 were excluded as they did not fulfil inclusion/exclusion criteria ($n = 8$ no BED; $n = 5$ ADHD; $n = 3$ BMI; $n = 2$ bariatric surgery; $n = 1$ seizure; $n = 1$ implausible symptoms). Thus, 31 patients were included in the whole project and completed the assessments. Selection criteria for the subgroup of this study ($N = 16$) are described in detail in the section *data cleaning*.

Procedure

An overview of the study procedure is shown in **Figure 1**. Each of the three study appointments were at least one week apart. To control for circadian effects, all patients were invited to complete their assessments at the same time during the late afternoon/evening. To keep homeostatic effects constant, patients were instructed to fast for at least for 4 h prior to their appointments. This was confirmed through analyses of patients' blood sugar levels, as well as hunger levels using a visual analogue scale ranging from 0 cm (not hungry) to 10 cm (very hungry).

At the first study appointment (T0), height, weight and socioeconomic variables were assessed. Two structured clinical interviews for current eating disorders and other psychiatric comorbidities were conducted to control for inclusion and exclusion criteria (EDE, Hilbert et al., 2004; SCID-I, Wittchen et al., 1997). We modified the German Version of the EDE so that an average of one binge eating episode per week over a period of 3 months was necessary to diagnose BED, as in accordance with the DSM-5. To characterise the sample, patients filled out two standardised questionnaires, i.e., the Barrat Impulsiveness Scale (BIS-15; Meule et al., 2011) and the Three-Factor Eating Questionnaire (TFEQ; Pudel and Westenhöfer, 1989). During the T0 appointment, the experimental measurement of the food-modified antisaccade task with concurrent EEG was also conducted. During appointments T1 and T2, verum or sham tDCS was applied while executing the food-modified antisaccade task.

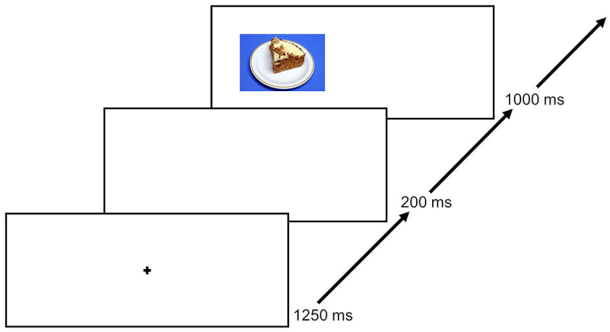

FIGURE 2 | An exemplary trial course. Each trial starts with a 1,250 ms lasting fixation, followed by a 250 ms ISI and thereafter a presentation of a food picture for 1,000 ms. Only food stimuli were used. The next trial starts again with the fixation. The figure was previously published by Max et al. (2021).

Questionnaires

Barratt Impulsiveness Scale (BIS-15)

Impulsivity as a personality trait was assessed using the BIS-15 (Meule et al., 2011). Three subscales characterise impulsivity: non-planning, motor and attentional impulsivity, while a total score is used as a marker of general impulsivity. A greater degree of impulsivity is indicated by a higher score on the corresponding scale.

Eating Disorder Examination (EDE)

The EDE is a semi-structured interview used to assess eating disorders (Hilbert et al., 2004). A total score indicates the severity of the total eating disorder pathology.

Three-Factor Eating Questionnaire (TFEQ)

Behavioural, cognitive and affective components of eating behaviour was assessed using the TFEQ (Pudel and Westenhöfer, 1989). Three subscales conceptualise the different facets of eating behaviour: restraint, disinhibition and hunger. The severity of each facet of eating behaviour is indicated by a higher score on the corresponding scale.

Food-Modified Antisaccade Task

This food-modified antisaccade task has been used in numerous studies (e.g., Schag et al., 2013; Leehr et al., 2018). An exemplary trial is shown in **Figure 2**. Patients in the current study were instructed to look at the fixation cross in the middle of the screen at the beginning of each trial for 1,250 ms. After an interstimulus interval (ISI) of 200 ms, a food picture was shown randomly on the left or right side of the screen for 1,000 ms. Each of the 40 food pictures was presented four times, counterbalanced on the left and right side of the screen throughout the experiment. Patients were instructed to look in the opposite direction of the picture as fast as possible after the food picture appeared on the screen (i.e., they were asked to perform an antisaccade). In total, each patient underwent 160 trials.

Stimuli and Stimulus Presentation

Forty coloured pictures of high-caloric food (400 x 295 pixels) served as stimulus material. The stimulus material depicted processed sweet or savory foods (e.g., chips, pizza, cookies, burger, chocolate). The stimuli were pre-tested in previous studies addressing response inhibition (Leehr et al., 2016; Giel et al., 2017a). The pictures were presented on a 15.6-inch laptop screen (1280 x 1024 pixels). The food pictures were rated on a visual analogue scale ranging from −5 to 5 concerning palatability ("very unappetizing" to "very appetizing"), wanting to eat the depicted food now ("not at all" to "very") and liking the food in general ("not at all" to "very").

Apparatus

Eye Tracking

Eye movements were recorded with SMI RED250mobile (250 Hz sampling rate, 0.4° gaze position accuracy) and iViewRed software. The mobile eye tracker was attached below the laptop screen and was placed 30 cm in front of the patient.

Eye Movement Data Processing

Raw data was analysed with BeGaze 3.7 using velocity-based default algorithms that detect fixations and saccades. MatLab R2017b (The Mathworks, Natick, MA, United States) was used for data cleaning and computing output variables, i.e., trial classification (correct vs. erroneous saccade). The error rate (saccades towards the food stimulus) was used as a marker of response inhibition (Hutton and Ettinger, 2006). A trial was excluded if participants did not look at the fixation cross at the beginning of a trial, if there were technical problems or if the saccades started below 80 ms or above 900 ms as these saccades were considered premature/delayed (Schag et al., 2013; Leehr et al., 2018). Single datasets from T0, T1 and T2 (verum or sham condition) with <30 valid eye tracking trials were discarded. The amount of included datasets are described in detail in the section data cleaning.

Electroencephalography Recording

The electroencephalogram (EEG) was recorded using an elastic cap (EASYCAP GmbH, Herrsching, Germany), the actiCHamp amplifier system with 32 active Ag/AgCl electrodes and the corresponding Brain Vision Recorder System (Brain Products GmbH, Gilching, Germany). Twenty seven scalp sites (FP1, F7, F3, Fz, F4, F8, FC5, FC1, FCz, FC2, FC6, C3, Cz, C4, CP5, CP1, CPz, CP2, CP6, P7, P3, Pz, P4, P8, O1, Oz, O2) were used to register the EEG. Two electrodes were placed about one centimetre left and right of the eyes for horizontal eye movements, another electrode was placed around one centimetre below the left eye and the FP1 electrode was used to detect vertical eye movements. One electrode was placed on each the left and the right mastoid. The left mastoid was used as an online reference, while the forehead electrode was used as a ground electrode. The online sampling rate was 1,000 Hz and impedances were kept below 10 kΩ before recording.

Electroencephalography Data Processing

EEG data was analysed using the MatLab R2017b EEGLAB toolbox (Delorme and Makeig, 2004) and the EEGLAB toolbox ERPLAB (Lopez-Calderon and Luck, 2014). Raw EEG data was resampled offline to 250 Hz and re-referenced to an average of the left and right mastoids. Multiple automated and manual artefact rejection was done (Luck, 2014): Butterworth band-pass filter with a low and high cut-off of 0.1 and 35 Hz and a Notch- filter at 50 Hz were applied. Artefacts were removed using automated independent component analysis (ICA, runica algorithm) (Winkler et al., 2011, 2014). Afterwards, ICA for artefact correction and artefact rejection were conducted manually through visual inspection by the author (Bİ) who was blinded to the experimental conditions. Stimulus locked epochs were extracted ranging from −100 to 1,000 ms, relative to the food picture stimulus. Behaviour locked epochs were extracted ranging from −100 to 500 ms, relative to a correct or erroneous saccade. A baseline correction with 100 ms before stimulus onset or behavioural onset was conducted within the epoched EEG. We decided to use a relatively short baseline to prevent the inclusion of visuomotoric preparation effects (Leehr et al., 2018). For the epoched EEG, artefact correction for the critical channels of the latter-built ERPs (see below) was conducted: Epochs containing EEG signals exceeding an amplitude of 65 μV within a 100 ms time window, or those exceeding −65 to +65 μV within the epoch were considered artefacts and were rejected.

According to the literature, ERPs are built out of three channels (see below). For each ERPs, we analysed mean amplitude, as this method is less noisy and more consistent than peak analyses (Luck, 2014). Time windows for the ERPs were based on visual inspection of ERPs waves, as well as the localisation and time course of the highest ERPs activity over the scalp (Luck, 2014). We excluded all patients with <8 valid ERPs epochs from erroneous or correct trials at T0 (see section data cleaning; Cohen and Polich, 1997; Olvet and Hajcak, 2009; Rietdijk et al., 2014). For the N2 analyses, the stimulus locked epochs were used and consisted of the average of the three frontocentral sites: Cz, Fz, Fcz (Espinet et al., 2012). We determined a time window ranging from 100 to 250 ms after stimulus onset which is in line with previous studies (Leehr et al., 2018; Biehl et al., 2020; Chami et al., 2020). The peaks of the ERP, as well as the highest N2 activity located frontocentral/posterior (Cz), further matched this time window. For the error-related negativity (ERN) behaviour locked epochs were used and consisted of the average of the three frontocentral sites: Cz, Fz, Fcz (Falkenstein et al., 1991). We determined a time window ranging from 50 to 150 ms after the behavioural onset which is in line with previous studies (Nieuwenhuis et al., 2001; Leehr et al., 2018). The highest frontocentral ERN activity for both correct and erroneous saccades were also within this time window. For the P3 analyses, the stimulus locked epochs were used and consisted of the average of the three centro-parietal sites: Cz, CPz, Pz (Sutton et al., 1965; Johnson, 1993; Sommer et al., 2021). We determined a time window ranging from 200 to 400 ms after stimulus onset, as the peaks of the ERPs as well as the highest parietal activity are located within this time window. This is somewhat earlier than what has been found in

previous studies (i.e. Lapenta et al., 2014; Biehl et al., 2020; Chami et al., 2020), but nevertheless within the normal range (see Luck, 2014).

Transcranial Direct Current Stimulation (tDCS)

Transcranial direct current stimulation (tDCS) was applied by two electrodes (5 x 7 cm) prepared with Ten20 conductive paste (Weaver and Company, Aurora, CO, USA). The electrodes were connected to a battery-driven, constant-current stimulator (DC-STIMULATOR MC, NeuroConn GmbH, Ilmenau, Germany). Placing the anodal electrode over the right dlPFC and the cathodal electrode on the left deltoid muscle, we aimed to increase excitability exclusively of the right dlPFC. The international 10–20 system of electrode placement helped to target the dlPFC by placing the anode over F4 (Jasper, 1958). For the placebo-condition, after the fade-in of 5 s the current was only applied for 46 s, resulting in typical perceived tDCS-sensations (e.g. tingling) and therefore serving as a valid placebo condition (Paulus, 2003).

TABLE 1 | Sample characteristics at baseline.

	N	M	SD
Age	16	38.6	13.6
BMI (kg/m^2)	16	33.7	10.9
binge eating episodes in the past 4 weeks acc. to EDE	16	15.6	13.4
EDE total score	16	2.0	.9
BIS-15 non-planning subscale	16	10.5	2.3
BIS-15 motor subscale	16	10.4	2.1
BIS-15 attentional subscale	16	8.5	2.5
TFEQ restraint	16	6.3	3.5
TFEQ disinhibition	16	11.3	3.2
TFEQ feeling hungry	16	10.3	2.5
Antisaccade task error rate (%) T0	16	47.6	26.2
Antisaccade task error rate (%) T1	16	40.5	30.4
Antisaccade task error rate (%) T2	15	40.0	26.2

BIS-15, baratt impulsiveness scale; EDE, eating disorder examination; TFEQ, three-factor eating questionnaire.

Data Cleaning

According to the exclusion criteria of eye tracking and EEG data, $n = 6$ patients had to be excluded from data analysis because of EEG artefact rejection, $n = 2$ because of <30 valid eye tracking trials at T0, $n = 1$ because of <8 valid epochs with correct saccades at T0, $n = 5$ because of <8 valid epochs with erroneous saccades at T0 and $n = 1$ because of corrupted EEG recording. Thus, a total of 16 patients could be included in the final data analyses. Concerning regression analyses, $n = 1$ patient was additionally excluded at T2/sham condition, because of <30 valid eye tracking trials, so that $n = 15$ patients were included in the respective regression analysis. Patients had on average $M = 100.8$ ($SD = 30.8$) valid eye tracking trials at T0, $M = 51.6$ ($SD = 33.8$) ERPs epochs from correct trials, as well as $M = 49.2$ ($SD = 32.6$) valid ERPs epochs from erroneous trials. Patients had $M = 106.7$ ($SD = 23.3$) valid eye tracking trials at T1/verum/sham condition and $M = 93.1$ ($SD = 37.0$) valid eye tracking trials at T2/sham/verum condition.

Statistical Analysis

All statistical inferences were conducted on a significance level of 95% using SPSS Statistics for Windows (version 24.0). As this is a pilot study, we did not want to inflate beta error propability so that we decided to correct for multiple comparisons only in the case of explorative and multiple testing (see hypothesis 3). To investigate differences in mean amplitudes of erroneous and correct saccades concerning the N2, P3 and ERN during the food-modified antisaccade task (hypothesis 1), paired two-tailed *t*-tests were conducted. Mean amplitudes of ERPs served as dependent variables. All ERPs variables were normally distributed. Sensitivity analyses with stricter cut-offs (N2: >20 trials, P3: >14 trials), other time windows (N2, P3) or single channels (P3 parietal activity) did not lead to deviating results.

Concerning hypothesis 2, we looked at the association between EEG activity and performance in the food-modified antisaccade task, as well as the predictive value of EEG activity on task performance at follow-up appointments (hypothesis 2), a stepwise statistical procedure was used, due in part to the small sample size. We computed correlations by Pearsons's correlation test between the mean amplitude of the ERPs variables (N2, P3 and ERN) in erroneous and correct saccade trials with the performance in the food-modified antisaccade task (mean percentage of erroneous saccades) at baseline and the follow-up appointments that were pooled for the stimulation condition (verum, sham). We further, computed correlations with the verum and sham condition that were pooled for the order of the follow-up appointments (T0, T1, T2). Thereafter we included the variables of the significant correlations stepwise into a regression model, while comparing the model-fits with ANOVA. In the regression analyses, we investigated erroneous saccades as outcome only at the follow-up assessments, not at baseline.

To investigate hypothesis 3, we looked at the association between EEG activity and clinical markers at T0 (eating pathology: EDE total score, binge eating frequency, BMI; trait impulsivity: BIS-15 subscales; food-related impulsivity: TFEQ subscales) by conducting Pearson's correlation tests. All variables were normally distributed besides binge eating frequency in the past four weeks. For the correlations with clinical markers, we Bonferroni-corrected for multiple testing with factor 3 as there were three different clinical markers (eating pathology, trait impulsivity, food-related impulsivity), resulting in a significance level of $p = 0.0167$.

RESULTS

Sample Characteristics and Stimulus Ratings

After data cleaning, 16 patients (14 female, two males) were included in the analyses. Further patient characteristics are described in **Table 1**. Paired two-tailed *t*-tests revealed that the antisaccade task error rate (%) at T1 did not significantly differ from T0 ($t_{(15)} = 1.60$, $p = 0.131$), nor did T1 significantly differ from T2 ($t_{(14)} = 0.82$, $p = 0.426$). The antisaccade task

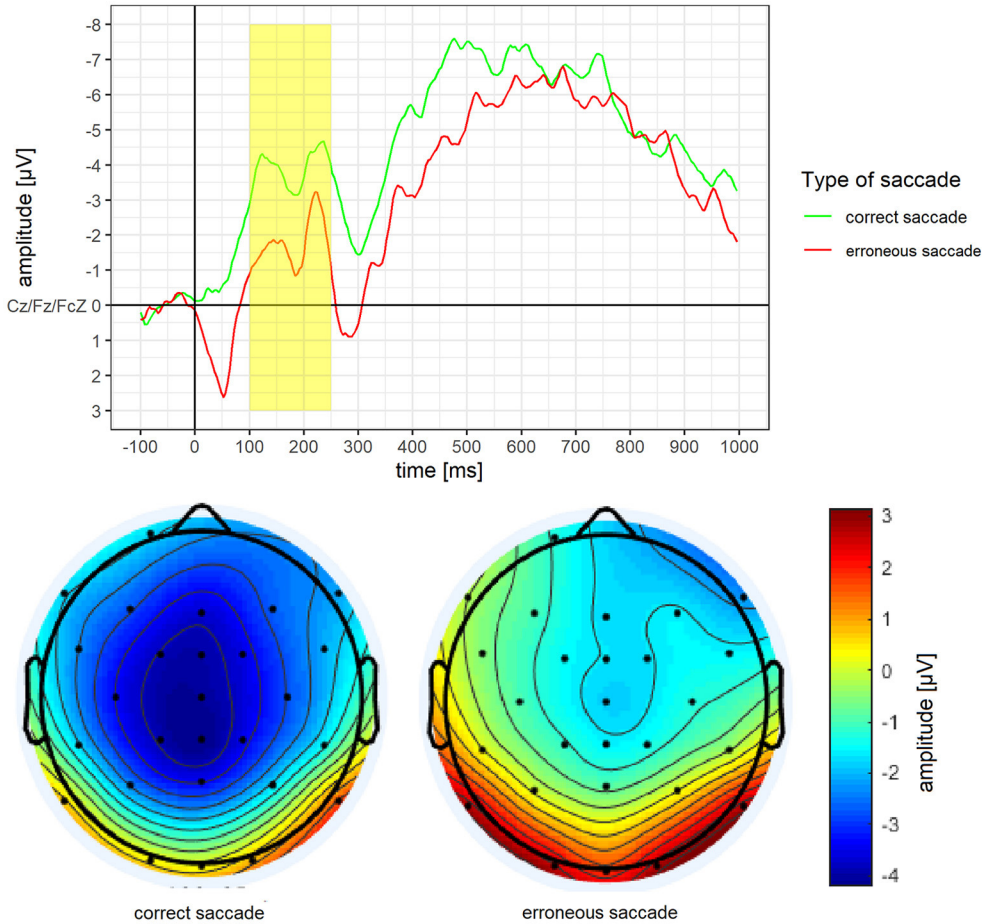

FIGURE 3 | Grand average difference wave of the N2 separately for erroneous and correct saccades. Underneath a scalp map displaying the mean voltage distribution for erroneous and correct saccades in the time window ranging from 100 to 250 ms after stimulus onset.

error rate (%) at T2 was significantly lower than at T0, $t_{(14)} = 2.38$, $p = 0.032$. An unpaired two-samples t-test revealed no significant difference between sham and verum stimulation, $t_{(9.89)} = -0.31$, $p = 0.762$. Concerning food valences, the stimuli were rated overall positively ($M_{\text{palatability}} = 1.60$, $SD_{\text{palatability}} = 2.56$; $M_{\text{wanting}} = 1.22$, $SD_{\text{wanting}} = 3.24$; $M_{\text{liking}} = 1.93$, $SD_{\text{liking}} = 2.96$).

Mean Amplitude of ERPs in Erroneous vs. Correct Saccades at Baseline

Mean amplitude and mean activity over the scalp for the N2 of erroneous and correct saccades are depicted in **Figure 3**. For the N2, a significantly less pronounced mean amplitude for erroneous saccades ($M = -1.74$ μV, $SD = 3.32$) than for correct saccades ($M = -3.90$ μV, $SD = 3.45$) was observed, $t_{(15)} = 3.46$, $p = 0.004$, $d = 0.86$.

Mean amplitude and mean activity over the scalp for the ERN of erroneous vs. correct saccades are depicted in **Figure 4**. For the ERN, a significantly more pronounced mean amplitude for erroneous saccades ($M = -2.87$ μV, $SD = 3.02$) than for correct saccades ($M = 0.62$ μV, $SD = 3.87$) was observed, $t_{(15)} = -3.37$, $p = 0.004$, $d = 0.84$.

Mean amplitude and mean activity over the scalp for the P3 of erroneous vs. correct saccades are depicted in **Figure 5**. For the P3, a significantly more pronounced mean amplitude for erroneous saccades ($M = 0.77$ μV, $SD = 2.63$) than for correct saccades ($M = -1.66$ μV, $SD = 4.22$) was observed, $t_{(15)} = 3.14$, $p = .007$, $d = 0.79$.

Associations Between ERPs and Performance in the Food-Modified Antisaccade Task at Baseline and Follow-Up Appointments

The correlations between ERPs and performance in the food-modified antisaccade task are shown in **Supplementary Table 1**. There were neither significant correlations between the N2 and the mean percentage of erroneous saccades nor between the ERN and the mean percentage of erroneous saccades. However, there were significant correlations between the mean amplitude of the P3 in erroneous saccades and the mean percentage of erroneous

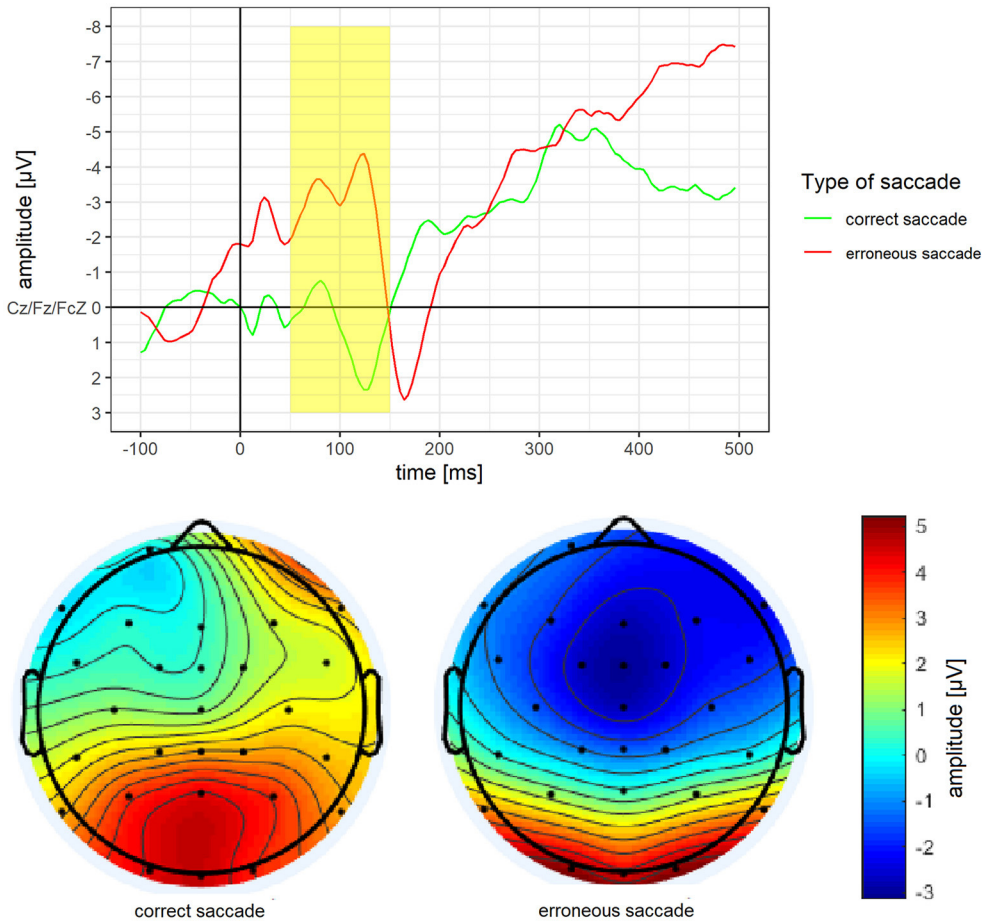

FIGURE 4 | Grand average difference wave of the ERN separately for erroneous and correct saccades. Underneath a scalp map displaying the mean voltage distribution for erroneous and correct saccades in the time window ranging from 50 to 150 ms after saccade onset.

saccades at T0 ($r = -0.64$, $p = 0.007$), T1 ($r = -0.65$, $p = 0.007$), T2 ($r = -0.64$, $p = 0.010$), under verum stimulation ($r = -0.67$, $p = 0.005$) and under sham stimulation ($r = -0.62$, $p = 0.015$). Furthermore, there were significant correlations between the mean amplitude of the P3 in correct saccades and the mean percentage of erroneous saccades at T0 ($r = -0.70$, $p = 0.002$), at T1 ($r = -0.52$, $p = 0.039$) and under verum stimulation ($r = -0.57$, $p = 0.022$), but no significant correlation with sham stimulation ($r = -0.43$, $p = 0.109$).

These significant correlations with the follow-up assessments were entered stepwise into linear regression analyses. The mean amplitude of the P3 in erroneous saccades significantly predicted the mean percentage of erroneous saccades at T1 ($\beta = -7.44$, $SE = 2.36$, $p = .007$), at T2 ($\beta = -6.23$, $SE = 2.06$, $p = 0.010$), under verum stimulation ($\beta = -7.22$, $SE = 2.14$, $p = 0.005$) and under sham stimulation ($\beta = -6.47$, $SE = 2.30$, $p = 0.015$).

Association Between ERPs and Clinical Markers at Baseline

All correlations between ERPs and clinical markers at baseline are presented in **Supplementary Table 2**. No significant correlations were observed between ERPs and eating disorder pathology (i.e., binge eating frequency, EDE scores, BMI). However, ERPs did partially correlate with trait impulsivity. The BIS-15 non-planning subscale showed a significant correlation with the mean amplitude of the N2 of correct saccades ($r = -0.59$, $p = 0.016$), the mean amplitude of the ERN of correct saccades ($r = -0.54$, $p = 0.032$) and the mean amplitude of the P3 of correct saccades ($r = -0.59$, $p = 0.017$). However, after Bonferroni-correction, only the association between the BIS-15 non-planning subscale and the N2 remained significant ($p < 0.0167$). While the N2 and ERN did not correlate with food-related impulsivity, a significant correlation could be found between the mean amplitude of the P3 in erroneous saccades and the TFEQ subscale restraint ($r = -0.61$, $p = 0.012$) as well as the subscale disinhibition ($r = -0.67$, $p = 0.004$).

DISCUSSION

This pilot study aimed to investigate the underlying neuropsychological mechanisms of an inhibitory control training combined with tDCS by analysing the ERPs (i.e., N2, ERN and P3) of patients with BED while executing the food-modified antisaccade task. Concerning hypothesis 1, we

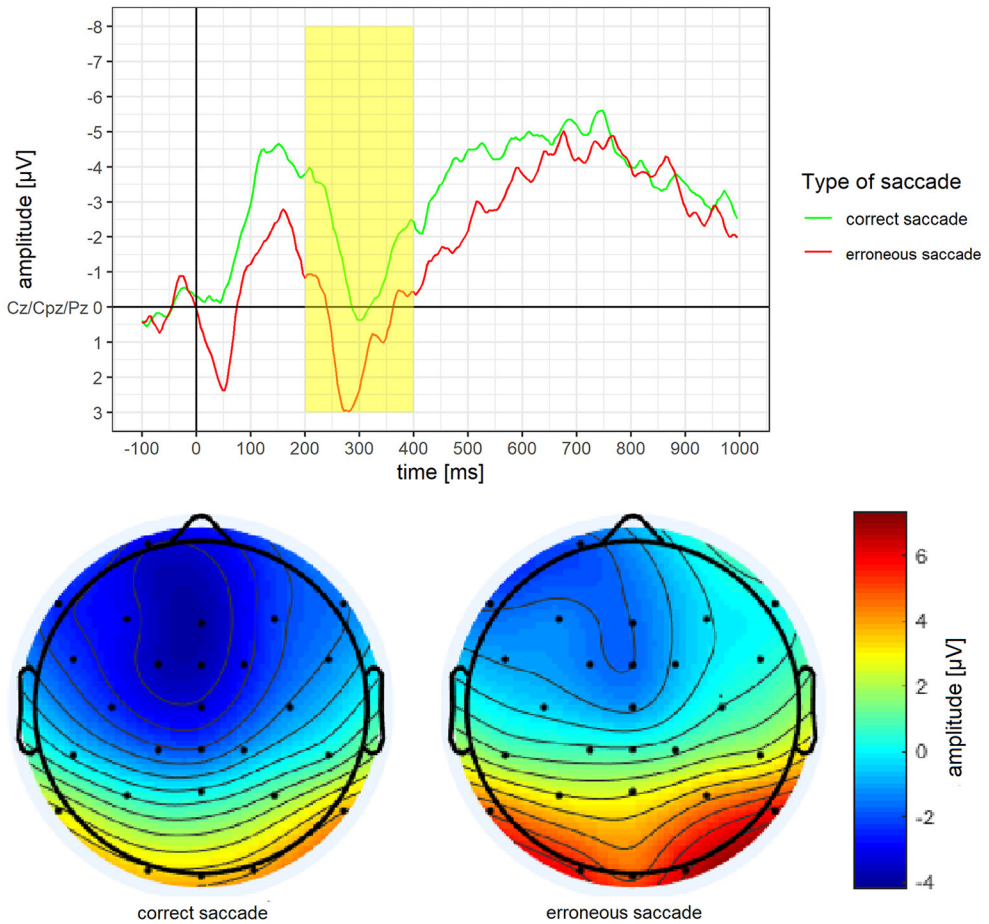

FIGURE 5 | Grand average difference wave of the P3 separately for erroneous and correct saccades. Underneath a scalp map displaying the mean voltage distribution for erroneous and correct saccades in the time window ranging from 200 to 400 ms after stimulus onset.

found significant differences between erroneous and correct saccades for the mean amplitudes of the ERPs. As expected, N2 mean amplitude was less pronounced in erroneous saccades vs. correct saccades, while ERN and P3 mean amplitudes were more pronounced in erroneous saccades vs. correct saccades. Concerning hypothesis 2, baseline P3 predicted the performance in the food-specific antisaccade task during verum and sham stimulation of the right dlPFC through tDCS at follow-up appointments. In terms of clinical markers (hypothesis 3), we demonstrated a significant association between N2 mean amplitude in correct saccades with non-planning behaviour of BIS-15, and between P3 mean amplitude in erroneous saccades with restraint and disinhibition of TFEQ.

Taking a closer look at our first hypothesis, N2 mean amplitude was significantly less pronounced in erroneous saccades vs. correct saccades indicating enhanced inhibition during correct saccades compared to erroneous saccades. This finding is consistent with previous research demonstrating increased N2 mean amplitudes in the case of increased cognitive conflict and difficulty in response inhibition (Chen et al., 2018). The ERN mean amplitude was significantly more pronounced in erroneous saccades vs. correct saccades with negative activity in erroneous saccades and positive activity in the correct saccades. This is in line with an earlier study combining EEG and ET (Leehr et al., 2018). After the ERN time window (around 150 to 200 ms), the peak from the erroneous trials changes and becomes as positive as the peak from the correct saccades. At this time, inhibition may be particularly pronounced, possibly during or else after correction of the error. This phenomenon could be explained by error positivity (Pe), which has been suggested to be responsible for error recognition and modification of response (Falkenstein et al., 2000; Nieuwenhuis et al., 2001). Thus, after an initially erroneous saccade, the behaviour might be corrected. These places demand on the neural capacities, demonstrated by an elevated ERN amplitude. Unfortunately, we were unable to investigate this hypothesis or further analyse error correction within our data, due to the small sample and frequency of trials. Meanwhile, P3 mean amplitude was significantly more pronounced in erroneous saccades than correct saccades. As previous research has demonstrated enhanced P3b amplitudes

towards attentional processing of salient stimuli, i.e., food vs. neutral stimuli (e.g., Nijs et al., 2008; Hill et al., 2013), it is possible that our study included assessments of the P3b component. Although the task required patients to look away from food stimuli, due to the rewarding and attention-grabbing properties of food (see Chami et al., 2019; Biehl et al., 2020), the effects of which are particularly amplified for patients with BED (e.g., Schag et al., 2013), attentional resources were more demanded in erroneous trials, when the patients looked at the food stimuli, i.e., were exposed to food.

Concerning our second hypothesis, task performance did not correlate with N2 or ERN mean amplitudes. This is in line with a previous study showing no effect of food-specific inhibitory control training on N2 amplitude (Carbine et al., 2021). However, the percentage of antisaccade errors in this study was highly correlated with the P3 mean amplitude of erroneous saccade trials, as well as partially correlated with correct saccade trials during T0, T1, T2 or during verum and sham stimulation. These findings suggest that if P3 mean amplitude is more pronounced at baseline assessment, the error rate in the inhibition task will be lower at the measurement points, independent from stimulation (verum or sham). While the comparisons between erroneous and correct saccades in hypothesis 1 were found for all patients, the correlations pertaining to hypothesis 2 were directly related to individual task-relevant performance with P3 activity. Thus, it may be possible that in assessing the P3, we assessed the attention-grabbing properties of food as well as inhibitory control mechanisms. Moreover, the regression analyses revealed that the mean amplitude of the P3 in erroneous saccades significantly predicted the error rates at T1 and at T2 under both, verum and sham stimulation. Thus, P3 could be interpreted as a predictor of the overall task performance as it predicts all measurement points and all stimulation conditions (see also results from Lapenta et al., 2014). This might imply that those who are already able to recruit resources for inhibitory control at baseline, might benefit more from such a training programme. This emphasises the neuromodulatory perspectives tDCS might offer in terms of facilitating inhibitory control. However, it is not possible to discriminate whether this effect was achieved due to training effects from the antisaccade task, tDCS stimulation or a combination of both. Given that P3 significantly predicted performance on both verum and sham conditions, it is more likely that the effect was independent of tDCS stimulation. In this regard, the efficacy of tDCS should be interpreted cautiously.

Our exploratory analysis concerning the third hypothesis, namely whether ERPs are associated with clinical markers of BED did not demonstrate a significant correlation between ERPs and frequency of binge eating episodes in the past four weeks, EDE total score or BMI. This is in accordance with previous research showing no significant association between P3 amplitude and eating psychopathology (Schaefer and Nooner, 2018; İceta et al., 2020). After Bonferroni correction, only N2 mean amplitudes in trials with correct saccades was negatively associated with non-planning behaviour, one facet of trait impulsivity (BIS-15). This is in line with the observation that the correlation between self-reported impulsivity and aspects of impulsive behaviour in a laboratory setting is rather low (Sharma et al., 2014). The strongest correlations between ERPs and self-reports within our study were found between P3 in erroneous saccade trials and food-related impulsivity (TFEQ), in particular with restraint and disinhibition subscales. These findings are further in line with those reported by Schag et al. (2021) who found significant correlations between the antisaccade task and food-related impulsive behaviour, but not with general eating pathology and trait impulsivity. Thus, a higher P3 activity in erroneous saccade trials is associated with less restraint, i.e., less cognitive control and thus more impulsive behaviour towards food. Surprisingly however, higher P3 activity is related as well to less disinhibition, i.e., less food-related impulsivity. This could be because all patients rated very high on this subscale with a mean of 11.5 ($SD = 3.2$), whereas a representative study from Löffler et al. (2015) reports a mean of 4.8 ($SD = 3.1$) for 40–50 year old females of the general population. Thus, within this patient group with very high disinhibition scores, those with less disinhibition had higher P3 activity while executing errors. A concern that has been raised by prior studies is that behavioural tasks and self-report improvements do not actually measure a single impulsivity frame (Sharma et al., 2014; Strickland and Johnson, 2020) and that objective measurements such as ERPs may be more accurate for testing inhibitory control towards food (Carbine et al., 2017). Overall, P3 might be closest to inhibitory control performance in the antisaccade task as it is a predictor for task performance at several study appointments. However, there is need for further investigating the role of P3 as potential marker for food-related inhibitory control processes.

Strengths and Limitations

Due to the low sample size and a considerable proportion of excluded patients and trials to increase data quality, the reported results are only preliminary and should be interpreted with caution. For instance, it could not be determined if stimulation intensity (1 mA vs. 2 mA) influenced the results. However, the error rate in the antisaccade task did not differ between 1 mA and 2 mA in the verum condition, thereby suggesting an independence of effects from stimulation. Another point is that P3 was assessed at centro-parietal sites, whereas a more frontal dlPFC area was stimulated with tDCS that is related with inhibitory control. This might explain why we observed not only inhibitory control, but also attention motivation processes with P3, while also explaining why P3 predicted task performance independently of verum vs. sham stimulation. Lastly, Barton et al. (2006) have argued that inhibitory processes are different for antisaccade and Go/No-go tasks. In this regard, the psychophysiological constructs that we assessed in this study might be different from previous studies that administered different tasks (e.g., Biehl et al., 2020; Chami et al., 2020; İceta et al., 2020), so that the results cannot be compared directly.

This study also contained several strengths. To the best of our knowledge, this pilot study is one of the rare studies investigating the psychophysiological processes of individuals with BED during a food-specific response inhibition task. A remarkable

strength is our investigation of the effect of neurostimulation with a combination of psychophysiological measures. Although studies on tDCS providing evidence for reducing food craving and binge eating behaviour are scarce, studies examining the effects of tDCS along with psychophysiological measures are virtually non-existent. A further strength of our study is the combination of psychophysiological measurement, behavioural task, and self-report instruments in the data collection. Furthermore, rather than relying on a self-report instrument for identifying individuals with BED, two structured clinical interviews were administered during the study.

Conclusions and Future Directions

This pilot study provides preliminary evidence for differing response inhibition processes among patients with BED when confronted with food through findings of less pronounced N2 and more pronounced ERN and P3 amplitudes in erroneous vs. correct saccades. As it predicts task performance on follow up assessments, P3 might be a potential marker for food-related inhibitory control processes in BED. As P3 predicted performance in the tDCS verum and sham conditions, there is no strong evidence based on this pilot study, that tDCS is a beneficial training adjunct in patients with BED. It might be that the response inhibition training itself might be solely benefial. However, based on previous literature suggesting that active tDCS can be helpful for reducing eating psychopathology (e.g., Burgess et al., 2016; Ljubisavljevic et al., 2016), a combined training consisting of the antisaccade task and anodal tDCS on the right dlPFC might target inhibitory control regions. To further investigate this question, if a combined training is more beneficial than the training task solely, we are currently running a randomised controlled trial (https://clinicaltrials.gov/ct2/show/study/NCT04572087) to enhance cognitive control over eating in patients with BED through six training sessions of anodal tDCS to the right dlPFC in combination with the food-related antisaccade task. Such a training might change underlying inhibitory control mechanisms of binge eating behaviour. For instance, those patients who are able to activate P3 areas from beginning on might benefit more from the training.

Another important point for the future are more neuromodulation studies on food-related impulsivity. Current studies in this field are providing promising findings regarding improve food intake, food craving, binge eating and response inhibition. Nevertheless, studies in patients with BED are too scarce to draw conclusion about their efficacy, and randomised controlled trial with this population are virtually non-existent (İnce et al., 2021). Moreover, the underlying mechanisms of neuromodulation are still not discovered and research concerning this topic is still in its infancy. Although our findings are encouraging, the results of the present pilot study nevertheless will need to be replicated with larger samples and with solutions to our previously described methodological challenges. Thus, we hope that our randomised controlled trial that is based on this project might be an initial step to elucidate the psychophysiological underpinnings of neurostimulation in patients with BED.

Concerning EEG research, previous literature has suggested that alternative interpretations, e.g., attentional bias to rewarding food stimuli, may also be possible. Further research is needed on this subject, given the preliminary nature of the data that is currently available. One such explanation pertains to late positive potentials as an interesting indicator of motivated attention towards salient stimuli (Svaldi et al., 2010; Carbine et al., 2020), which could enrich our understanding of electrophysiological phases of food cue processing. Based on previous research findings (e.g., Nijs et al., 2010; Nikendei et al., 2012; Seo and Lee, 2021), future research might also benefit from investigating whether homoeostasis or shape and weight concern modify electrophysiological and behavioural response inhibition among individuals with BED.

Taken together, our pilot study delivers first insights into the psychophysiological processes of patients with BED while executing a response inhibition task. Our results will engage further research concerning underlying mechanisms and potential interventions in patients with BED.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The study was approved by the Ethics Committee of the Medical Faculty Tübingen, Germany (Project No. 459/2016BO2). The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

KG, CP, KS, and SZ contributed to the study conception and design. Material preparation, data collection, and analysis were performed by SM with support from KS. EL provided the procedure and programme codes for the recording, cleaning and aggregation of EEG data and gave valuable support concerning EEG data. EEG processing was done by SM with support from Bİ and KS. The first draft of the manuscript was written by Bİ, SM, and KS and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpsyg.2021.721672/full#supplementary-material

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9.3. Noch nicht eingereichte Manuskripte

Behavioural biases in the interaction with food objects in virtual reality and its clinical implication for the binge eating disorder

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Abstract

Cognitive processes play a central role in the development, maintenance as well as the remission in several mental disorders, like in Binge Eating Disorder (BED). Insights into cognitive mechanisms reflected by embodied interaction with food and its connections to clinically relevant psychopathology offer new possibilities for translational diagnostics and interventions of BED. To this end, we longitudinally investigated differential effects in the manual interaction with food in a virtual reality (VR) setup in 31 patients (M_{age} = 36.26, M_{BMI} = 35.02) with BED. Patients were assessed at baseline before participating in a randomized-controlled trial (RCT) and at a six-week follow-up. At both assessments, the patients underwent an experimental VR paradigm and were characterized concerning eating disorder psychopathology, eating behaviour, general impulsivity and food craving by questionnaires and semi-structured clinical interviews. In the experimental task, the patients had to collect one of two simultaneously presented objects (food vs. office tools). At both assessments, patients recognized food faster than office tools and subsequent approach behaviour was initiated faster, whereas after movement initiation, food was collected slower than office tools. No relationship between behavioural biases, operationalized by a differential manual interaction pattern with food compared to office tools, and sample characterizations (e.g. eating disorder psychopathology, food craving, impulsivity) could be detected. In sum, the study emphasizes two different stages in the manual interaction with food: A faster first stage that comprises recognition and movement initiation and a slower second stage that comprises controlled handling and may reflect aversive motivational processes. However, as the behavioural patterns do not change with an observed ameliorated psychopathology of BED at the second assessment, the task seems insensitive in detecting translational interconnections between behavioural biases and eating disorder pathology, impulsivity, eating behaviour and food craving. Future research should focus on multimethod approaches to investigate underlying neurophysiological processes to get a broader view on various facets of BED.

1. Introduction

Since 2013 Binge Eating Disorder (BED) is a distinct eating disorder according to the Fifth Edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5). Since then, diverse studies investigate underlying cognitive mechanisms, and their role in the development, maintenance as well as remission of BED [1,2]. Further, especially if disorder-relevant stimuli (e.g. food) are involved, cognitive functions like inhibition, working memory, memory are impaired on a behavioural and neurophysiological level, indicating an association between BED and disorder-specific difficulties in cognitive domains and highlighting the relevance of addressing impaired cognitive functions in appropriate interventions in BED [3]. However, data on aspects of embodiment as reflected for instance by the specific dynamics of physical interaction with food stimuli, is scarce.

A core characteristic of BED is the recurrence of binge eating episodes and loss of control without inappropriate compensatory behaviours (e.g. fasting, purging, excessive exercise). Two theoretical frameworks seem suitable to explain the core symptom of BED. First, a dual-process system consisting of an impulsive system and a reflective system [4,5]. The impulsive system mainly evaluates environmental cues regarding emotional and motivational relevance, whereas the reflective system comprises mainly deliberate processes like cognitive control which also considers long-term consequences. Especially in BED, a stronger impulsive system and a weaker reflective system leads to increased impulsivity and poor cognitive control towards food stimuli [6,7,3]. Another framework highlights food-related impulsivity as a central factor in BED: increased sensitivity to rewarding stimuli, increased rash and spontaneous behaviour towards rewarding stimuli or slower disentanglement of those [8,9]. In sum, attentional biases for food indicate faster processing of food in an early orientation reaction and slower disengagement from these stimuli in patients with BED, thus suggesting to interfere with response inhibition and goal-directed behaviour [10-15].

Especially if food stimuli are involved, research has shown that several cognitive domains in patients with BED are altered compared to healthy controls: decreased mental flexibility [16], impaired response inhibition [17,11,18,19], reduced visual disengagement from food [20,14], decreased cognitive control [21] and elevated rapid orientation towards food [15,13]. These altered cognitions were shown to be associated with the severity of BED symptoms [22,12], Body-Mass-Index (BMI) [23] or general impulsivity [24]. Further, reduction of these attentional biases by application of a cognitive training or a psychotherapy intervention showed also a reduction in eating disorder symptoms and food craving, highlighting the strong interconnection between psychopathology and cognition [25-27].

Whereas most experimental paradigms measure exclusively cognitive domains, virtual reality (VR) in combination with motion tracking allows to investigate more complex appetitive behaviour like grasping movements and their hypothesized underlying cognitive processes. In this connection, embodied cognitions play a central role. Within the concept of embodied cognitions it is assumed, that the agent's physical body causally contributes to cognitive processes [28]. Previously it could be shown, that in a non-clinical population food stimuli is more prominent in the manual interaction than the control stimuli and this effect are more prominent in the VR compared to a 2D-touchscreen application, supporting the hypothesis of embodied cognitions [29,30]. In the study of Max et al. (2021), the participants had to detect and collect the target out of two concurrently presented stimuli. Food was detected faster than office tools but collected slower afterwards. Stronger behavioural control towards food was observed, and this was associated with an increased activity in the right dorsolateral prefrontal cortex (dlPFC).

To validate and explore the clinical implication of these findings, we set out to investigate the VR paradigm in a sample with BED. Patients underwent the binary-choice-forced-choice paradigm at two times: Before the participation in a clinical randomised controlled trial (RCT) and four weeks after finishing the RCT. In this RCT, patients with diagnosed BED underwent six sessions of a cognitive training to increase inhibitory control towards food in an antisaccade paradigm which was combined either with sham or verum stimulation using transcranial direct current stimulation (tDCS) (https://clinicaltrials.gov/ct2/show/study/NCT04572087). In the current project, we explore the differential effects in the manual interaction with food in the VR in a repeated-measure design. Because of its salient and rewarding nature especially in patients with BED, we expect faster movement initiation towards food than towards office tools at the first measurement [31-33]. Further, as BED is characterized by reduced cognitive control and increased impulsive eating behaviour, we expect faster handling of food than of office tools at the first measurement. After the cognitive training and the associated expected improvement in eating disorder pathology, this behavioural pattern should change at the second measurement, resulting in slower, thus less impulsive interaction with food. To explore the clinical implications of the task, we investigate if the behavioural patterns in the interaction with food are linked with eating disorder psychopathology, general impulsivity, cognitive and behavioural domains of eating behaviour and food craving at the first measurement. If there is a causal connection between behavioural biases and the facets of psychopathology, impulsivity, eating behaviour and food craving, the behavioural biases should predict just those facets assessed either by self-reported

questionnaires or semi-structured clinical interviews. Further, if these behavioural patterns are contributing factors in the development and maintenance of BED, changed behavioural patterns at the second measurement in relation to the first measurement should predict the change of above-mentioned facets of psychopathology, impulsivity, eating behaviour and food craving at the second measurement in relation to the first measurement.

2. Methods

2.1. Participants

All patients had to fulfil the criteria for BED according to DSM-5 [34]. The first 32 patients who gave informed consent were recruited from a randomised controlled trial (https://clinicaltrials.gov/ct2/show/study/NCT04572087). This sample size was chosen in accordance with the pilot-study with healthy subjects [29]. From the first 32 patients, one patient was excluded as the patient dropped out during the intervention. Thus, 31 patients (24 women, M_{age} = 36.26, SD_{age} = 13.37, M_{BMI} = 35.02, SD_{BMI} = 9.72) completed both appointments of the study. Exclusion criteria were current or lifetime psychotic disorder, bipolar-I disorder, current substance dependence, current suicidality, previous bariatric surgery, severe somatic diseases which influence weight or eating behaviour and are not controlled by stable medication, severe neurologic disease and impaired vision, ametropia, eye diseases which prevent the execution of the task. For their completion of both study appointments the patients received 20€. The study was approved by the ethics committee of the Medical Faculty Tübingen (043/2020BO2) and all participants gave informed consent.

2.2. Apparatus

2.2.1. Virtual Reality (VR).

The patients wore a head-mounted display (HMD) with continuous tracking of head rotation and interindividual adjusted inter-pupillary distance (Oculus Rift CV1; Oculus VR, Inc., Menlo Park, USA). Both screens of the HMD had a resolution of 1080x1200 pixels. The virtual environment was built and controlled by Unity 3D (5.6.2f1) with a bundled version of OVRPlugin. Trajectories of the patients' hand were tracked by a near-infrared sensor (Leap Motion Inc., San Francisco, USA) and were streamed in real-time into the HMD. Thus, the patients could interact with the virtual stimuli by actual movements of their hand. The sensor was placed on a small table in front of the patients and covered a range of approximately 1600 cm^2 of the patients' dominant hand. The 3D-stimuli of a previous study were used [29]. The

stimuli consisted of 48 different variations stemming from 3 categories (balls, food, office objects). Each stimulus was rated concerning valence, arousal, urge to grasp, aesthetics, subjective estimated size and comfort of grasping at the first and second experimental measure, see Inline Supplementary Table 1 and Inline Supplementary Table 2.

--- Insert Supplementary Table 1 here ---

--- Insert Supplementary Table 2 here ---

2.3. Procedure

The study consisted of two measurements with at least six weeks in between the appointments. In between the appointments the patients participated in a study examining the clinical effects of a cognitive training on BED (https://clinicaltrials.gov/ct2/show/study/NCT04572087). The procedure of both appointments was identical. Three hours prior to the experiment the patients were instructed to be fasted. At the experimental measure this was checked by self-report and each patient declared conformity with this instruction. Before the first appointment which mainly comprised the behavioural task in the VR, demographic data, weight and height measured on a scale, the diagnosis and severity of the BED examined by the Eating Disorder Examination (EDE; [35]), Three-Factor Eating Questionnaire (TFEQ; [36]), Barratt Impulsiveness Scale (BIS-15; [37]), UPPS Impulsiveness Scale (UPPS; [38]) were assessed at the baseline of the clinical trial which was conducted 1 to 14 days (M_{days} = 2.91; SD_{days} = 2.59) before the first appointment. At the second appointment the above-mentioned data was assessed prior to the behavioural task in the VR. Food-Craving was measured by the Food-Craving Questionnaire-State [39] before and after the behavioural task.

For the behavioural task in the VR, the patients were equipped with the HMD and completed practice trials to get familiar with operating the system. Patients had to put their dominant hand in a standardized start position to start a trial. The start position was marked by seven red coloured spheres which turned green if the hand was placed in the right position. Afterwards, the crosshair of the HMD had to be aligned with a fixation cross for at least one second. With a stimulus onset asynchrony of 400 milliseconds, one target and one distractor stimulus were presented concurrently next to each other. If the patients moved their hand before

the presentation of the stimuli, an error message was displayed. The positions of target and distractor stimulus were counterbalanced on the left and right table. A trial was finished when the target stimulus was grasped and placed inside the box. If the target stimulus was placed outside of the box, the wrong stimulus was grasped or the grasping took longer than five seconds, and error message was displayed and the trial was discarded. The spatial distance between start position and target stimulus was approximately 40 cm. The whole behavioural task consisted of six blocks with 32 trials each. In two blocks each a certain stimulus category had to be grasped according to the visually presented block instruction: food, balls or office tools. Each stimulus category was selected twice as a target and as a distractor and were paired with each other counterbalanced and within the stimulus category each variation of the stimulus category was presented randomized and balanced on the left and right table. Across patients block order was counterbalanced and patients were allocated randomized to a block order. In total, the task took about 15 minutes. An exemplary trial is shown in figure 1. After the behavioural task, each presented stimulus was rated. In total, each of the two appointments took about 60 minutes.

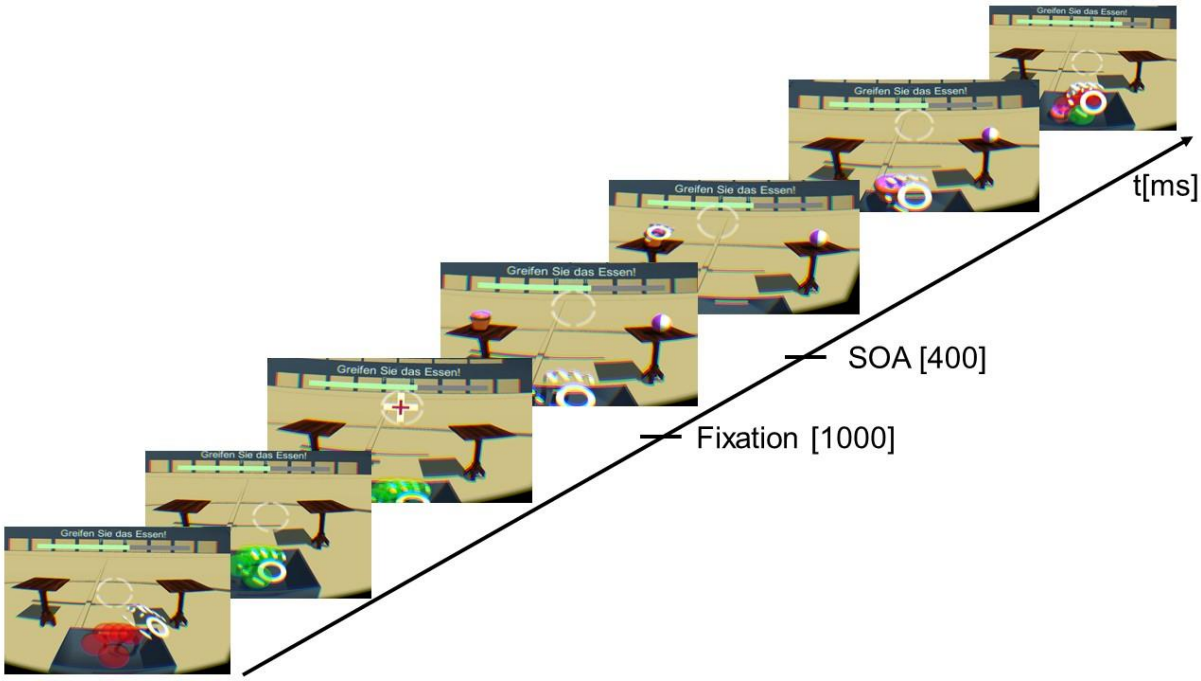

Figure 1. Visualization of a trial of the condition “food”. The target stimulus to be grasped was a chocolate cupcake with pink icing. After matching the initial hand pose with the standardized hand pose, the crosshair of the HMD had to be aligned with the fixation cross for one second. After 400 milliseconds, target and distractor stimulus were presented on the left and right table. The image was previously used by Max et al. (2021).

2.4. Materials

2.4.1. Eating Disorder Examination (EDE)

The EDE is a structured clinical interview to examine various eating disorders (Binge-Eating Disorder, Bulimia Nervosa, Anorexia Nervosa) and is adapted to the criteria of the DSM-5 [35]. It allows the quantification of a specific eating disorder pathology. The EDE consists of four subscales (restraint, eating concern, weight concern, shape concern). Restraint comprises the attempt to restrict food intake and to diet. Eating concern is characterized by other abnormalities concerning eating like intrusive thoughts concerning eating. Weight-related worries are depicted by the subscale weight concern, like the impact of weight on the self-worth. Shape concern is operationalized similar to weight concern. Furthermore, a total score indicates the severity of eating disorder pathology [35]. For each scale, a higher score indicates a higher markedness of the corresponding scale.

2.4.2. Food-Craving Questionnaire-State (FCQ-S)

The FCQ-S assesses the desire to eat a specific food as a state variable. 15 items subdivide into three subscales: intense desire to eat/loss of control, positive affect and hunger [39]. Furthermore, a total score operationalizes a current food craving. For each scale, a higher score indicates a higher degree of food craving.

2.4.3. Three Factor Eating Questionnaire (TFEQ)

The TFEQ operationalizes eating behaviour on three scales: restraint, disinhibition and hunger. Restraint includes dieting and avoidance of high-calorie food. Disinhibition comprises habitual, emotional and situational susceptibility. Hunger captures internal and external processing of hunger cues [36]. A higher score indicates a higher markedness of the eating behaviour component.

2.4.4. Barratt Impulsiveness Scale (BIS-15)

The BIS-15 assesses impulsivity, the drive to act fast and thoughtlessly without taking negative consequences into account. The BIS-15 [37] comprises 15 items which subdivide into the subscale attentional impulsivity, motor impulsivity and non-planning impulsivity. For each scale, a higher score indicates a higher degree of impulsivity.

2.4.5. UPPS Impulsiveness Scale (UPPS)

The UPPS operationalizes impulsivity on four scales: urgency, lack of premeditation, lack of perseverance and sensation seeking. Urgency reflects the tendency to follow impulses evoked by negative affect. Premeditation captures the tendency to act deliberately and consciously. The ability to stay focussed on a challenging task is covered by perseverance. Sensation seeking refers to the tendency enjoying risky and exciting activities [38]. A higher score on each scale reflects a higher markedness of the different faces of impulsivity.

2.5. Data analysis and statistics

2.5.1. Behavioural data analysis.

For every statistical test a significance level of 5 % was used. To check for the efficacy of the training intervention, paired t-Tests were performed on the overall score of the EDE and number of binge eating episodes during the last four weeks, an indicator for the general eating disorder pathology. On a behavioural level, incorrect trials in the VR were excluded from all analyses (0.16%). Incorrect trials were defined as follows: For the movement onset, reaction times above 2000 ms and below 200 ms as well as reaction times above 4000 ms for the collection time were considered premature/incorrect as a result of visual inspection. Further, values deviating more than 2.5 *SD* from individual cell mean were considered outlier responses (3.71%). We standardized the reaction times for the food- and office-objects in relation to the ball-objects to account for individual differences in motor grasping of grasp-affordant objects. For each trial the individual's mean reaction time for ball objects was subtracted. Concerning the first hypothesis, we accounted for individual differences in grasping food stimuli by using a linear mixed model approach. All linear mixed models were calculated by the *lme4*-package of R [40]. Log-likelihood-tests between a linear mixed model with the fixed effect and a linear mixed model without the fixed effect were conducted to determine significance. Two fixed effects were tested within the linear mixed model: Time (*T0* vs. *T1*) and the category of the target stimuli (*Food* vs. *Office tools*). To test the contrasts within the levels of the fixed effects, the *lsmeans*-package of R was used, based on the method of the least-squares means and adjusted by Tukey method [41]. To estimate effect sizes for fixed effects f^2 was used which can also be used in mixed linear models [42,43].

For the second hypothesis, multivariate linear regression was conducted. An individual bias of the manual actions for each patient was calculated by the difference of the ball standardized reaction times of food objects and the ball standardized reaction times of office tools:

$(RT_{Office} - RT_{Ball}) - (RT_{Food} - RT_{Ball})$.

Those individual biases were used as a predictor variable for the different markers of eating disorder pathology (EDE), eating behaviour (TFEQ), food craving (FCQ-S) and impulsivity (BIS-15, UPPS) at T0.

For the third hypothesis, the approach of the second hypothesis was used. However, a difference score between T0 and T1 was calculated for the individual biases of the manual actions and the different markers of eating disorder pathology, eating behaviour, food craving and impulsivity. A negative difference score represents a decrease in the individual bias and the different markers.

3. Results

3.1. Change in Eating Disorder Psychopathology

At T1, general eating disorder psychopathology (M = 2.04, SD = 0.85) was significantly lower than at T0 (M = 2.61, SD = 0.89), $t(30) = 5.41$, $p < .001$, $d = 0.65$. The same applied to the number of binge eating episodes in the last four weeks. At T1, significantly fewer binge eating episodes (M = 6.26, SD = 6.66) were reported compared to T0 (M = 17.35, SD = 10.74), $t(30) = 5.53$, $p < .001$, $d = 1.24$.

3.2. Effects of Food on Different Stages of Manual Action in VR

3.2.1. Movement onset.

Including the category of target stimuli as a fixed effect in the mixed model leads to a significantly better model than the random intercept-only model, $\chi^2(1) = 109.21$, $p < .001$, $R^2 = .09$. The movement onset for the food-objects as a target was significantly faster than for the office-tool-objects (M = 28.11 ms), $t = 10.49$, $p < .001$, $f^2 = .015$.

Including time as fixed effects in the mixed model does not lead to a significantly better model than the random intercept-only model, $\chi^2(1) = 0.02$, $p = .897$, $R^2 = .08$. In figure 2 the ball-object-corrected reaction times of the movement onset are depicted. For the raw reaction times of the movement onset, see Inline Supplementary Table 3.

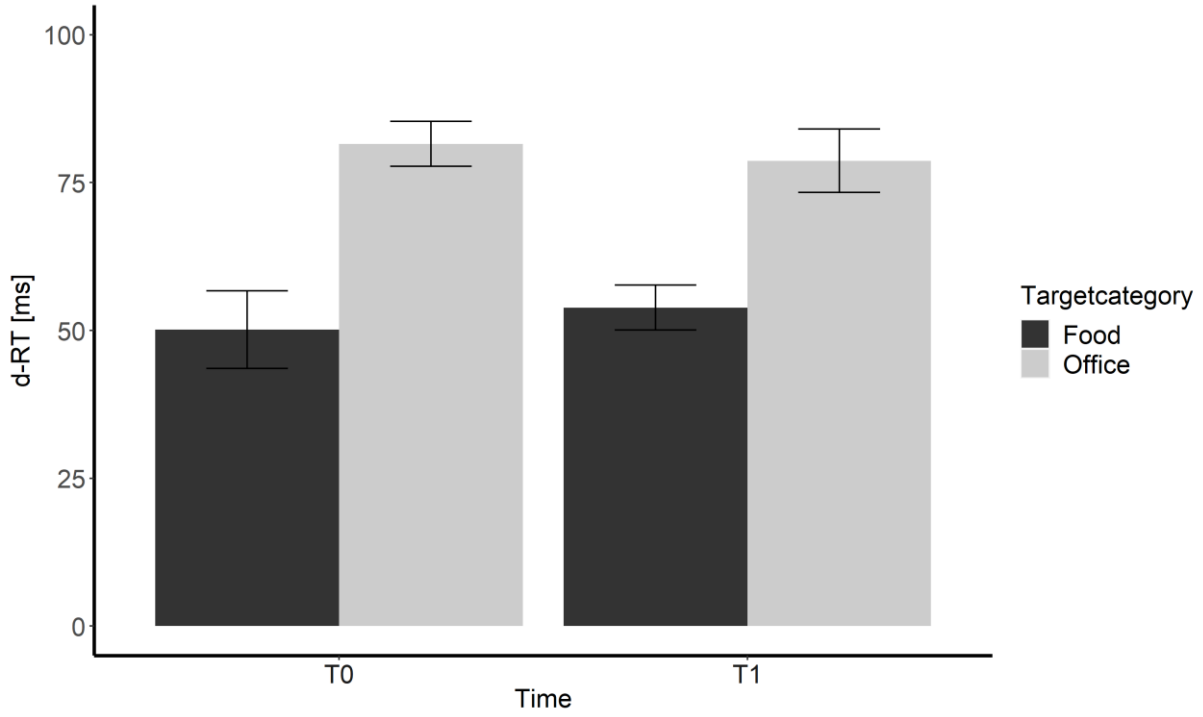

Figure 2. Movement onset in relation to the movement onset reaction times of the ball-objects. The bars represent the standard error. d-RT were calculated by subtracting the reaction time of the target stimulus from the reaction time of the ball objects.

--- Insert Supplementary Table 3 here ---

3.2.2. Collection time.

Including the category of target stimuli as fixed effects in the mixed model leads to a significantly better model than the random intercept-only model, $\chi^2(1) = 50.48$, $p < .001$, $R^2 = .19$. Including the time as a fixed effect leads to a significantly better model than the random intercept-only model, $\chi^2(1) = 49.27$, $p < .001$, $R^2 = .11$. Those two fixed effects do not interact with each other, as including two fixed effects as an interaction doesn't lead to a better model than two isolated fixed effects, $\chi^2(1) = 0.03$, $p = .858$, $R^2 = .19$. Thus, food-objects were collected significantly slower than office-tool-objects ($M = 48.10$), $t = 7.12$, $p < .001$, $f^2 = .007$. Furthermore, the collection time of the target stimuli was significantly faster at T0 compared to T1 ($M = 27.25$), $t = 4.02$, $p < .001$, $f^2 = .003$. As soon as the participants have left their initial hand position, they collected office-objects quicker than food-objects and an overall faster collection time from T1 to T0 irrespective of the target category could be observed. In figure 3 the ball-object-corrected reaction times of the collection time are depicted. For the raw reaction times of the collection time, see Inline Supplementary Table 3.

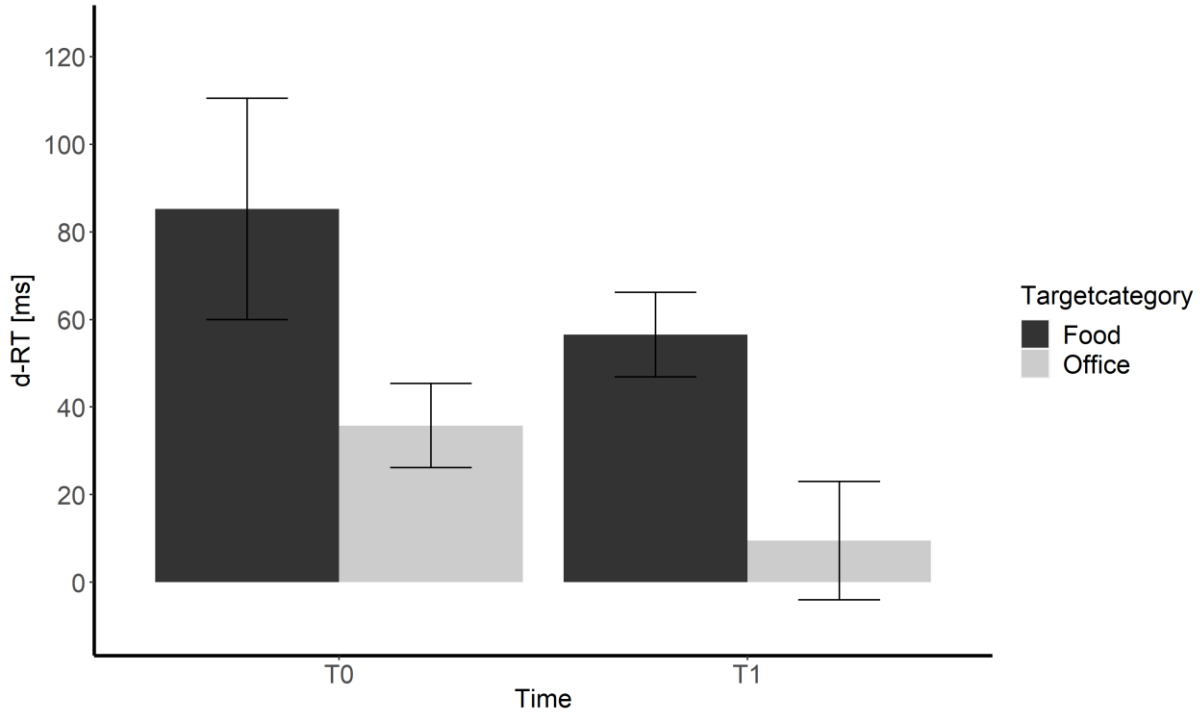

Figure 3. Collection time in relation to the movement onset reaction times of the ball-objects. The bars represent the standard error. d-RT were calculated by subtracting the reaction time of the target stimulus from the reaction time of the ball objects.

3.3. Individual bias of manual actions and markers of psychopathology, eating behaviour, food craving and impulsivity at T0

No markers concerning eating disorder psychopathology, eating behaviour or impulsivity at T0 were predicted by the behavioural patterns in the manual interaction with the food objects at T0. All estimates of the behavioural biases on the markers can be looked up in Table 1.

Table 1

Multiple linear regression of individual biases of manual actions on markers of psychopathology, eating behaviour, food craving and impulsivity at T0

	Movement Onset Bias	**Collection Time Bias**
FCQ Total Score	β = -0.022, t = -0.84, p = .411, R^2 = .02	β = 0.011, t = 1.24, p = .227, R^2 = .05
FCQ Desire to eat/Loss of control	β = -0.010, t = -0.88, p = .384, R^2 = .03	β = 0.006, t = 1.38, p = .178, R^2 = .06
FCQ Reinforcement/positive affect	β = -0.010, t = -0.88, p = .385, R^2 = .03	β = 0.003, t = 0.84, p = .407, R^2 = .02
FCQ Hunger	β = -0.002, t = -0.27, p = .787, R^2 = .002	β = 0.002, t = 1.12, p = .271, R^2 = .04
BIS Total Score	β = 0.020, t = 1.52, p = .139, R^2 = .07	β = 0.007, t = 1.49, p = .147, R^2 = .07
BIS Non-Planning Impulsivity	β = 0.006, t = 0.97, p = .339, R^2 = .03	β = 0.002, t = 0.92, p = .364, R^2 = .03
BIS Motor Impulsivity	β = 0.007, t = 1.30, p = .203, R^2 = .06	β = 0.003, t = 1.71, p = .099, R^2 = .09
BIS Attentional Impulsivity	β = 0.007, t = 1.18, p = .248, R^2 = .05	β = 0.002, t = 0.81, p = .424, R^2 = .02
EDE Total Score	β = -0.002, t = -0.93, p = .363, R^2 = .03	β = 0.001, t = 1.08, p = .287, R^2 = .04
EDE Restraint	β = 0.000, t = 0.22, p = .830, R^2 = .001	β = 0.001, t = 1.04, p = .308, R^2 = .04
EDE Eating Concern	β = 0.001, t = 0.26, p = .800, R^2 = .002	β = 0.001, t = 1.29, p = .208, R^2 = .05

EDE Weight Concern	β = -0.002, t = -1.01, p = .322, R^2 = .03	β = 0.0002, t = 0.33, p = .746, R^2 = .004
EDE Shape Concern	β = -0.005, t = -1.96, p = .059, R^2 = .12	β = 0.001, t = 0.63, p = .533, R^2 = .01
EDE number of binge eating episodes during the last 4 weeks	β = -0.039, t = -2.00, p = .055, R^2 = .12	β = -0.005, t = -0.74, p = .467, R^2 = .02
TFEQ restraint	β = 0.004, t = 0.49, p = .628, R^2 = .01	β = -0.0003, t = -0.10, p = .918, R^2 = .0003
TFEQ disinhibition	β = 0.002, t = 0.52, p = .609, R^2 = .01	β = 0.003, t = 1.74, p = .093, R^2 = .10
TFEQ hunger	β = -0.006, t = -1.06, p = .296, R^2 = .04	β = 0.001, t = 0.33, p = .745, R^2 = .003
UPPS Urgency	β = 0.001, t = 1.10, p = .282, R^2 = .04	β = 0.0002, t = 0.55, p = .586, R^2 = .01
UPPS Lack of premeditation	β = 0.002, t = 1.87, p = .072, R^2 = .11	β = 0.0004, t = 1.40, p = .173, R^2 = .06
UPPS Lack of perseverance	β = 0.002, t = 1.47, p = .153, R^2 = .07	β = -0.001, t = 1.72, p = .096, R^2 = .10
UPPS Sensation seeking	β = -0.002, t = -1.35, p = .186, R^2 = .06	β = -0.001, t = -1.92, p = .065, R^2 = .11
BMI	β = -0.017, t = -0.93, p = .361, R^2 = .03	β = -0.002, t = -0.33, p = .744, R^2 = .004

Note. Estimates, *t*-values and R^2 of the different individual biases are reported.

3.4. Changes of individual biases of manual actions and changes of markers of eating behaviour, food craving and impulsivity

No changes in the markers concerning eating disorder psychopathology, eating behaviour or impulsivity at T1 in relation to T0 were predicted by the changes of behavioural patterns in the manual interaction with the food objects at T1 in relation to T0. All predictors of the multiple linear regression are listed in Table 2.

Table 2

Multiple linear regression of changes concerning individual biases of manual actions on changes in markers of psychopathology, eating behaviour, food craving and impulsivity

	ΔMovement Onset Bias	**ΔCollection Time Bias**
ΔFCQ Total Score	β = -0.031, t = -1.08, p = .290, R^2 = .04	β = -0.001, t = -0.11, p = .911, R^2 = .0004
ΔFCQ Desire to eat/Loss of control	β = -0.015, t = -1.06, p = .296, R^2 = .04	β = -0.002, t = -0.47, p = .639, R^2 = .008
ΔFCQ Reinforcement/positive affect	β = -0.018, t = -1.56, p = .130, R^2 = .08	β = -0.002, t = -0.47, p = .645, R^2 = .01
ΔFCQ Hunger	β = 0.003, t = 0.45, p = .657, R^2 = .006	β = 0.003, t = 1.33, p = .193, R^2 = .06
ΔBIS Total Score	β = -0.006, t = -0.40, p = .695, R^2 = .01	β = 0.004, t = 0.95, p = .350, R^2 = .03
ΔBIS Non-Planning Impulsivity	β = -0.005, t = -0.65, p = .523, R^2 = .01	β = 0.004, t = 1.66, p = .109, R^2 = .08
ΔBIS Motor Impulsivity	β = -0.003, t = -0.43, p = .672, R^2 = .01	β = -0.004, t = -1.75, p = .092, R^2 = .10
ΔBIS Attentional Impulsivity	β = 0.002, t = 0.24, p = .816, R^2 = .001	β = 0.004, t = 1.19, p = .243, R^2 = .05
ΔEDE Total Score	β = -0.0001, t = -0.03, p = .998, R^2 = .0001	β = 0.0002, t = 0.51, p = .612, R^2 = .01
ΔEDE Restraint	β = 0.002, t = 0.76, p = .456, R^2 = .02	β = -0.00003, t = -0.04, p = .971, R^2 = .00004
ΔEDE Eating Concern	β = 0.0004, t = 0.13, p = .896, R^2 = .001	β = 0.001, t = 0.82, p = .422, R^2 = .02

ΔEDE Weight Concern	β = -0.001, t = -0.36, p = .719, R^2 = .004	β = -0.0002, t = -0.41, p = .686, R^2 = .01
ΔEDE Shape Concern	β = -0.002, t = -0.84, p = .407, R^2 = .02	β = 0.0004, t = 0.63, p = .533, R^2 = .01
ΔEDE number of binge eating episodes during the last 4 weeks	β = -0.041, t = -1.59, p = .122, R^2 = .08	β = 0.001, t = 0.24, p = .812, R^2 = .002
ΔTFEQ restraint	β = -0.009, t = -0.86, p = .396, R^2 = .02	β = -0.004, t = -1.16, p = .255, R^2 = .04
ΔTFEQ disinhibition	β = 0.007, t = 1.00, p = .325, R^2 = .03	β = 0.0005, t = 0.21, p = .838, R^2 = .001
ΔTFEQ hunger	β = -0.004, t = -0.72, p = .478, R^2 = .02	β = -0.001, t = -0.28, p = .779, R^2 = .003
ΔUPPS Urgency	β = -0.001, t = -1.25, p = .220, R^2 = .05	β = -0.10, t = -1.81, p = .081, R^2 = .10
ΔUPPS Lack of premeditation	β = 0.001, t = 1.62, p = .116, R^2 = .08	β = 0.0004, t = 0.00, p = 1, R^2 < .0001
ΔUPPS Lack of perseverance	β = 0.0001, t = -0.06, p = .951, R^2 = .0001	β = 0.0001, t = 0.26, p = .798, R^2 = .002
ΔUPPS Sensation seeking	β = -0.002, t = -0.25, p = .801, R^2 = .002	β = -0.0001, t = -0.44, p = .660, R^2 = .007
ΔBMI	β = -0.0001, t = -0.06, p = .955, R^2 = .0001	β = 0.0003, t = 0.47, p = .643, R^2 = .008

Note. Estimates, *t*-values and R^2 of the different individual biases are reported.

4. Discussion

The present study revealed differential effects in the manual interaction with food in VR in a clinical sample with BED. In line with our hypothesis, we found faster movement initiation towards food than towards office tools at the first measurement. In contradiction to our expectation, we did not observe faster handling of food than of office tools, as office tools were actually collected faster than food, consistent with the finding in healthy subjects [29]. Further, even if the BED psychopathology of the patients significantly decreased from T0 to T1, the behavioural patterns in the interaction with food compared to office tools did not change. At T1, still a significantly faster movement initiation towards food than towards office tools could be observed, whereas office tools were still collected faster than food. No link between markers of eating disorder pathology, impulsivity, eating behaviour, food craving and behavioural patterns in the interaction with food reached statistical significance.

A central finding is the faster movement initiation towards food than towards office tools. This first stage of manual interaction comprises a complex interplay between motoric and cognitive systems. On the one hand, out of two concurrently objects the target has to be recognized and categorized, on the other hand a goal-directed behaviour towards the target has to be initiated. This is in line with the assumption, that especially in BED, strong impulsive responses towards food stimuli can be observed and those stimuli are processed faster than other stimuli [15,13]. Thus, predisposed impulsive behaviour coupled with faster processing of food stimuli leads to faster movement initiation towards food also in this new paradigm in VR. Surprisingly, in contradiction of the assumption of generally elevated food-related impulsivity in patients with BED, food was collected slower than office tools after an approach movement was initiated [8,9]. Even though this finding is unexpected, it coincides with the finding of the study of Max et al. (2021) with healthy participants. In this study, a slower collection time of food compared to office tools could be observed. It was hypothesized, that the slower collection time may reflect a more cautious handling due to increased personal relevance. The slower collection time could also mirror a certain ambivalence towards food experienced by patients with BED as it has been previously shown in terms of an approach-avoidance-conflict using psychophysiological measures [44,45]. Alternatively, it may be the case, the patients in this study also wanted to make sure, that the highly-hedonic stimuli are collected cautiously without getting lost. As the target had to be identified explicitly and may be categorized as a problematic object, an aversive motivational process may impede a fast collection.

Concerning behavioural patterns in the manual interaction with food, we tried to identify differential effects in the manual interaction due to generally changed psychopathology of the

BED due to the participation in a treatment trial. In fact, the general eating disorder pathology as well as the frequency of binge eating episodes significantly decreased from T0 to T1 after the cognitive training and independent from tDCS stimulation. Even if the psychopathology changed, no changes in the behavioural pattern in the manual interaction with food could be observed, as no interaction effect became evident. The behavioural patterns at T1 were comparable to the behavioural patterns at T0: In the first stage of manual interaction, compared to office tools, the categorization of food and movement initiation towards it was faster, whereas in the second stage, food was collected slower than office tools.

To have a closer look into the interconnection between psychopathology of the BED and behavioural patterns in the manual interaction with food, we ran a multiple regression with markers of psychopathology, eating behaviour, food craving and impulsivity. The interconnection between the psychopathology and behavioural pattern in the experimental VR task seems to be rather scarce as we did not find any statistical significant prediction of the markers of psychopathology, eating behaviour, food craving and impulsivity by behavioural biases in the interaction with food. By using a repeated-measure within-subject design we were able to have an insight into the impact of changed behavioural markers in the interaction with food on altered markers of eating disorder psychopathology, impulsivity, food craving and eating behaviour on an individual level. Still, we were not able to find an association between changes on a behavioural level and changes on an eating disorder pathology level. This contradicts the assumption, that there is a strong interconnection between markers of psychopathology and task performance in a laboratory setting [25,26]. As there is a great variety of experimental tasks used and the tasks greatly differ from each other, the task used in the present study seems to be inappropriate to uncover this interconnection. Taken together, the findings concerning the clinical implications of the task used in the current study may be supported by studies, that emphasize the missing validity between laboratory tasks and self-report instruments [46]. Already in well-established experimental paradigms, a missing interconnection between laboratory task performance and general eating disorder pathology or trait impulsivity could be observed [47].

One strength of this pilot study is the repeated-measure within-subject design, assessing the subjects before and after a clinical intervention, which ameliorated eating disorder psychopathology of the BED. Thus, we could have drawn precise conclusions concerning contributing factors in the development, maintenance or remission of the BED and behavioural patterns in a laboratory task in the VR. Findings of a repeated measure within a person in a state of clinical relevant BED compared to ameliorated psychopathology give a deeper insight into

possible underlying mechanisms than comparing it to a matched control group. Another strength of the study is the usage of VR, which allows to investigate manual interaction with food in an experimentally controlled environment. Thus, a more ecologically valid situation could be created, where patients could interact with food by using their actual hands instead of the commonly used button presses on keyboards. Last, the findings of the pilot-study concerning the behavioural patterns in the manual interaction with food could be replicated, emphasizing that this newly paradigm captures two different stages. A fast, impulsive first stage, where food is recognized faster and consequently movement towards food is initiated faster, and a slower, more controlled second stage, where food is collected slower and more cautiously. In this connection, the new paradigm does not seem to be sensitive to specific symptoms of BED, as the several assessed markers were not predicted by the behavioural biases in the interaction with food. Further, healthy participants showed a similar behavioural pattern in the interaction with food as the patients with BED, even if a statistical comparison between the two groups would not be reasonable due to differences in the design, programming of the task and missing demographic matching between the two groups [29]. Nonetheless, even if there is an absence of significant effects between the clinical markers of the BED and the behavioural patterns in the VR, discrete or more complex interconnections cannot be excluded as the sample size was rather small and many associations reached trending statistical significance. Future research using VR to explore the manual interaction with food and its clinical implications may profit from focusing on underlying neurophysiological processes to have a multimethod approach on assessing psychopathology-related biases by using neuroimaging (functional near-infrared spectroscopy, electro-encephalography) and neuromodulatory (transcranial direct current stimulation, transcranial magnet stimulation) techniques.

5. Conclusion

In sum, this study could demonstrate two different stages in the manual interaction with food in patients with BED and replicate a behavioural pattern that has been found in a previous study with healthy participants: A first stage, where food as a target is recognized faster and movement towards food is initiated faster than for office tools and a second stage, where food is collected slower than office tools, thus reflecting more cautious handling which might be explained by ambivalence or aversive motivational processes like avoidance. However, this behavioural pattern does not change with an ameliorated psychopathology of BED. Therefore,

this paradigm does not seem sensitive enough to detect interconnections between eating disorder pathology, impulsivity, eating behaviour, food craving and the behavioural patterns in the VR. More insight into underlying motivational processes in the manual interaction with food and its underlying neurophysiological processes is needed to draw a more overall picture on the associations between neurophysiological, clinical and behavioural markers in the BED.

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Inline Supplementary Tables

Table 1

Ratings of VR stimuli at T0

Stimulus	Mean Valence (SD)	Mean Arousal (SD)	Mean Urge to grasp (SD)	Mean Aesthetics (SD)	Mean subjective Size (SD)	Mean Grasp Comfort (SD)
Baseball	**57.67 (16.50)**	**47.89 (18.52)**	**54.6 (18.20)**	**57.67 (16.50)**	**48.51 (18.01)**	**65.14 (16.84)**
Baseball_1	61.58 (16.93)	47.19 (19.20)	54.87 (18.37)	61.58 (16.93)	51.16 (20.71)	63.58 (18.23)
Baseball_2	55.77 (22.72)	48.23 (25.21)	55.26 (23.11)	55.77 (22.72)	47.06 (21.14)	65 (21.78)
Baseball_3	57.1 (20.48)	46.74 (21.47)	54.35 (20.53)	57.1 (20.48)	50.68 (22.14)	66.26 (18.01)
Baseball_4	56.23 (17.12)	49.39 (21.74)	53.9 (20.37)	56.23 (17.12)	45.13 (17.56)	65.71 (18.57)
Beachball	**52.94 (15.35)**	**46.52 (16.99)**	**54.73 (20.59)**	**52.94 (15.35)**	**57 (18.89)**	**63.57 (20.03)**
Beachball_1	56.48 (18.48)	47.74 (20.15)	60.26 (24.51)	56.48 (18.48)	59.55 (21.66)	63.68 (21.73)
Beachball_2	51.55 (19.85)	47.52 (22.41)	53.84 (24.90)	51.55 (19.85)	57.1 (23.31)	66.81 (24.45)
Beachball_3	55.32 (23.62)	46.71 (21.94)	53.87 (21.78)	55.32 (23.62)	54.87 (20.92)	64 (22.89)
Beachball_4	48.42 (18.26)	44.1 (20.05)	50.94 (24.90)	48.42 (18.26)	56.48 (20.64)	59.81 (22.91)
Handball	**53.92 (15.02)**	**49.74 (20.09)**	**54.84 (19.03)**	**53.92 (15.02)**	**59.46 (16.76)**	**65.23 (19.19)**
Handball_1	57.81 (20.89)	52.03 (23.08)	56.42 (19.95)	57.81 (20.89)	61.03 (16.25)	66.42 (17.40)
Handball_2	43.42 (24.57)	46.74 (25.16)	50.9 (21.74)	43.42 (24.57)	60.48 (18.86)	62.61 (22.39)
Handball_3	57.19 (22.22)	53.03 (22.20)	55.13 (23.01)	57.19 (22.22)	59.55 (20.19)	63.97 (23.49)
Handball_4	57.26 (19.88)	47.16 (22.82)	56.9 (23.20)	57.26 (19.88)	56.77 (20.80)	67.94 (21.71)
Tennisball	**57.79 (13.28)**	**47.53 (20.84)**	**57.23 (21.46)**	**57.79 (13.28)**	**48.23 (20.14)**	**65.45 (18.83)**
Tennisball_1	55.81 (22.07)	48.71 (22.31)	63.26 (23.08)	55.81 (22.07)	49.32 (22.37)	67.32 (19.68)
Tennisball_2	61.42 (19.15)	48.45 (26.75)	56.81 (25.25)	61.42 (19.15)	46.32 (21.48)	65.06 (21.12)
Tennisball_3	57.35 (18.90)	42.97 (23.23)	55.48 (23.56)	57.35 (18.90)	48.32 (23.74)	67.03 (21.85)
Tennisball_4	56.58 (20.50)	50 (25.42)	53.35 (27.05)	56.58 (20.50)	48.97 (21.24)	62.39 (21.84)
Burger	**53.87 (19.49)**	**53.68 (15.22)**	**58.48 (19.92)**	**53.87 (19.49)**	**58.33 (15.29)**	**60.27 (18.28)**
Burger_1	47.84 (26.41)	52.35 (24.87)	58.19 (23.14)	47.84 (26.41)	58.45 (21.64)	62.19 (22.59)
Burger_2	55.16 (23.02)	52.03 (19.42)	58.48 (20.82)	55.16 (23.02)	57.32 (19.07)	58.74 (21.67)
Burger_3	63.26 (18.31)	60.23 (16.91)	64.58 (22.59)	63.26 (18.31)	62.52 (14.02)	65.52 (18.31)
Burger_4	49.23 (24.94)	50.1 (25.73)	52.68 (27.62)	49.23 (24.94)	55.03 (22.49)	54.61 (24.27)
Cupcake	**63.51 (15.91)**	**59.08 (17.18)**	**59.26 (21.08)**	**63.51 (15.91)**	**52.31 (17.03)**	**63.52 (17.54)**
Cupcake_1	66.35 (16.51)	60.26 (20.88)	62.29 (24.58)	66.35 (16.51)	53.29 (18.85)	61.65 (20.56)
Cupcake_2	64.74 (18.63)	61.32 (19.62)	58.03 (24.33)	64.74 (18.63)	53.87 (20.29)	66.06 (20.49)
Cupcake_3	59 (23.25)	55.71 (23.03)	57 (23.20)	59 (23.25)	53.52 (17.58)	63.9 (19.93)
Cupcake_4	63.94 (19.07)	59.03 (18.21)	59.71 (22.73)	63.94 (19.07)	48.55 (21.65)	62.48 (18.92)

Donut	**64.43 (16.36)**	**58.3 (16.86)**	**58.81 (21.78)**	**64.43 (16.36)**	**53.1 (17.61)**	**64.56 (19.17)**
Donut_1	61.77 (19.87)	54.03 (21.78)	54.84 (26.53)	61.77 (19.87)	50.74 (19.34)	65.1 (21.61)
Donut_2	62.35 (24.51)	56.03 (22.39)	57.81 (25.78)	62.35 (24.51)	52.61 (21.56)	63.58 (22.96)
Donut_3	65.55 (17.11)	62.06 (18.70)	62.48 (22.13)	65.55 (17.11)	53.65 (20.76)	62.03 (23.28)
Donut_4	68.03 (17.56)	61.06 (19.32)	60.13 (24.83)	68.03 (17.56)	55.42 (21.52)	67.52 (16.78)
Pizza	**59.14 (18.26)**	**58.31 (13.13)**	**62.35 (16.64)**	**59.14 (18.26)**	**65.94 (14.30)**	**62.56 (18.32)**
Pizza_1	61.19 (18.28)	59.26 (17.05)	62.58 (18.61)	61.19 (18.28)	66.39 (15.28)	63.06 (20.02)
Pizza_2	60.45 (22.18)	58.48 (15.03)	64.42 (19.72)	60.45 (22.18)	68.39 (13.93)	60.87 (20.53)
Pizza_3	54.32 (25.05)	55.94 (21.05)	61.1 (22.65)	54.32 (25.05)	63.16 (18.07)	61.81 (22.77)
Pizza_4	60.58 (19.51)	59.55 (14.81)	61.32 (16.73)	60.58 (19.51)	65.84 (17.57)	64.52 (20.13)
Calculator	**50 (16.43)**	**40.55 (19.68)**	**48.98 (20.01)**	**50 (16.43)**	**49.65 (15.95)**	**57.91 (18.31)**
Calculator_1	43.84 (23.96)	34.94 (23.19)	46.68 (24.98)	43.84 (23.96)	49.19 (18.09)	55.97 (20.18)
Calculator_2	58.9 (24.44)	49.61 (24.40)	51.16 (21.77)	58.9 (24.44)	52.77 (17.69)	58.61 (23.64)
Calculator_3	51.65 (22.87)	42.1 (21.68)	52.65 (25.39)	51.65 (22.87)	50.23 (20.76)	55.84 (23.41)
Calculator _4	45.61 (24.16)	35.55 (23.18)	45.42 (24.56)	45.61 (24.16)	46.39 (18.15)	61.23 (20.71)
Folder	**53.68 (15.49)**	**41.48 (18.16)**	**52.89 (21.19)**	**53.68 (15.49)**	**66.5 (15.26)**	**58.25 (20.82)**
Folder_1	46.32 (19.81)	35.13 (20.67)	48.68 (21.38)	46.32 (19.81)	65.35 (17.46)	56.19 (21.86)
Folder_2	60.32 (26.23)	46.06 (23.04)	55.9 (25.12)	60.32 (26.23)	67.06 (20.45)	56.35 (25.83)
Folder_3	56.9 (19.06)	44.32 (24.49)	54.45 (26.22)	56.9 (19.06)	66.1 (16.55)	62.42 (22.23)
Folder_4	51.16 (18.67)	40.42 (20.23)	52.52 (24.72)	51.16 (18.67)	67.48 (14.82)	58.03 (22.77)
Hole-puncher	**39.54 (15.35)**	**34.43 (16.71)**	**44.34 (19.54)**	**39.54 (15.35)**	**59.56 (12.52)**	**54.55 (17.40)**
Hole-puncher_1	41.1 (16.74)	35.42 (19.63)	45.55 (22.27)	41.1 (16.74)	57.61 (15.91)	52.29 (18.90)
Hole-puncher_2	41.68 (22.67)	36.97 (19.31)	43.52 (22.85)	41.68 (22.67)	62.39 (18.94)	56.48 (19.22)
Hole_puncher_3	40.71 (19.95)	33.48 (23.03)	43.81 (24.34)	40.71 (19.95)	58.19 (14.72)	55 (19.13)
Hole_puncher_4	34.68 (21.90)	31.84 (20.70)	44.48 (26.78)	34.68 (21.90)	60.06 (17.95)	54.42 (20.79)
Stapler	**45.85 (16.55)**	**40.72 (18.91)**	**47.15 (20.90)**	**45.85 (16.55)**	**48.09 (13.62)**	**54.46 (19.97)**
Stapler_1	44.13 (21.31)	39.45 (23.08)	48.26 (22.54)	44.13 (21.31)	46.65 (16.49)	54.55 (22.06)
Stapler_2	46.71 (20.43)	40 (21.93)	49.26 (24.16)	46.71 (20.43)	48.1 (17.34)	53.74 (22.00)
Stapler_3	46.97 (18.60)	43.06 (20.13)	44.32 (23.62)	46.97 (18.60)	48.58 (15.47)	55.35 (20.72)
Stapler_4	45.58 (21.09)	40.35 (20.45)	46.74 (24.84)	45.58 (21.09)	49.03 (19.53)	54.19 (22.98)

Note. Ratings on VR stimuli were reported on a visual analogue scale ranging from 0 to 100. 100 is reflecting a high score on the corresponding scale, whereas 0 is reflecting a low score. Mean ratings and standard deviations per category and per item are reported.

Table 2

Ratings of VR stimuli at T1

Stimulus	Mean Valence (SD)	Mean Arousal (SD)	Mean Urge to grasp (SD)	Mean Aesthetics (SD)	Mean subjective Size (SD)	Mean Grasp Comfort (SD)
Baseball	**53.46 (15.52)**	**46.26 (17.78)**	**50.7 (22.80)**	**53.46 (15.52)**	**48.33 (15.93)**	**62.04 (20.75)**
Baseball_1	58.03 (14.99)	47.81 (21.29)	49.58 (24.60)	58.03 (14.99)	50.29 (18.17)	64.71 (22.91)
Baseball_2	50.84 (22.49)	46.68 (22.74)	51.03 (24.74)	50.84 (22.49)	46.74 (18.84)	58.81 (22.45)
Baseball_3	49.45 (20.68)	43.03 (19.61)	52.48 (24.52)	49.45 (20.68)	47.87 (19.31)	61.74 (24.12)
Baseball_4	55.52 (17.49)	47.52 (20.07)	49.71 (24.44)	55.52 (17.49)	48.42 (18.44)	62.9 (21.88)
Beachball	**55.6 (16.91)**	**46.01 (18.20)**	**52.73 (23.26)**	**55.6 (16.91)**	**59.44 (14.92)**	**62.6 (22.84)**
Beachball_1	60.94 (20.44)	46.65 (21.96)	54.32 (25.27)	60.94 (20.44)	59.52 (17.31)	60.77 (24.05)
Beachball_2	54.94 (18.11)	44.45 (21.57)	50.42 (24.06)	54.94 (18.11)	60.55 (19.94)	63.87 (24.34)
Beachball_3	53.45 (20.23)	48.77 (18.76)	52.65 (22.75)	53.45 (20.23)	56.61 (18.59)	62.9 (23.80)
Beachball_4	53.06 (23.10)	44.16 (23.12)	53.55 (25.58)	53.06 (23.10)	61.06 (15.67)	62.87 (25.18)
Handball	**52.49 (17.64)**	**45.21 (19.42)**	**51.41 (21.95)**	**52.49 (17.64)**	**58.93 (12.13)**	**63.89 (21.16)**
Handball_1	50.97 (22.58)	45.74 (24.13)	54.39 (24.54)	50.97 (22.58)	58.74 (17.18)	64.55 (23.24)
Handball_2	48.94 (23.49)	40.03 (22.01)	50.13 (26.10)	48.94 (23.49)	59.06 (16.10)	62.61 (22.94)
Handball_3	56.1 (24.53)	49.03 (22.42)	49.48 (24.25)	56.1 (24.53)	57.87 (18.79)	65.58 (23.05)
Handball_4	53.97 (20.69)	46.03 (22.01)	51.65 (22.62)	53.97 (20.69)	60.03 (15.57)	62.81 (22.91)
Tennisball	**52.6 (13.79)**	**45.3 (19.06)**	**48.56 (22.36)**	**52.6 (13.79)**	**48.95 (16.13)**	**62.6 (19.13)**
Tennisball_1	49.13 (22.47)	41.77 (22.92)	47.39 (25.20)	49.13 (22.47)	43.03 (17.67)	59.32 (21.59)
Tennisball_2	54.77 (21.31)	47.29 (20.88)	47.68 (25.37)	54.77 (21.31)	47.65 (18.70)	60.65 (23.90)
Tennisball_3	57.84 (17.83)	47.42 (22.85)	50.97 (24.04)	57.84 (17.83)	54.68 (20.60)	68.29 (20.84)
Tennisball_4	48.65 (20.16)	44.71 (21.96)	48.23 (24.26)	48.65 (20.16)	50.45 (21.48)	62.13 (23.49)
Burger	**51.73 (18.32)**	**52.73 (18.73)**	**54.38 (22.39)**	**51.73 (18.32)**	**62.25 (14.08)**	**59.72 (20.09)**
Burger_1	51.97 (23.53)	53.23 (21.01)	52.42 (22.72)	51.97 (23.53)	60.84 (17.17)	60.42 (23.03)
Burger_2	53.16 (24.02)	51.16 (21.12)	54.65 (25.89)	53.16 (24.02)	61.77 (17.50)	59.61 (23.21)
Burger_3	52 (20.26)	52.35 (22.43)	56.71 (23.41)	52 (20.26)	62 (16.03)	62.16 (25.93)
Burger_4	49.77 (19.77)	54.16 (21.56)	53.74 (22.85)	49.77 (19.77)	64.39 (14.17)	56.68 (20.83)
Cupcake	**54.02 (19.43)**	**52.64 (18.71)**	**48.61 (22.63)**	**54.02 (19.43)**	**48.67 (14.21)**	**57.98 (21.36)**
Cupcake_1	56.65 (21.78)	53.48 (21.09)	49.29 (25.06)	56.65 (21.78)	48.52 (17.82)	59.26 (21.92)
Cupcake_2	54.19 (19.75)	50.68 (22.37)	46.19 (24.43)	54.19 (19.75)	49.45 (15.24)	58.32 (23.22)
Cupcake_3	49.45 (25.06)	48.45 (21.58)	47.61 (24.76)	49.45 (25.06)	47.97 (15.40)	56.48 (23.96)
Cupcake_4	55.77 (20.59)	57.94 (20.26)	51.35 (24.45)	55.77 (20.59)	48.74 (17.06)	57.87 (23.60)

Donut	**57.82 (19.92)**	**53.87 (20.06)**	**52.64 (23.69)**	**57.82 (19.92)**	**51.69 (12.87)**	**59.75 (20.70)**
Donut_1	54.61 (23.88)	52.74 (21.65)	51 (25.07)	54.61 (23.88)	51.1 (17.11)	58.81 (22.42)
Donut_2	55.29 (20.51)	52.71 (21.15)	50.23 (24.03)	55.29 (20.51)	50.84 (16.44)	57.26 (21.12)
Donut_3	63.16 (21.95)	56.29 (24.68)	56.26 (25.58)	63.16 (21.95)	50.77 (20.48)	61.06 (21.35)
Donut_4	58.23 (25.23)	53.74 (22.69)	53.06 (26.73)	58.23 (25.23)	54.06 (14.50)	61.87 (24.97)
Pizza	**51.6 (18.99)**	**51.44 (19.63)**	**53.21 (23.58)**	**51.6 (18.99)**	**62.35 (16.00)**	**57.3 (21.81)**
Pizza_1	53.48 (22.53)	51 (22.28)	56.35 (24.26)	53.48 (22.53)	64.55 (17.59)	57 (23.50)
Pizza_2	49.71 (24.30)	50.13 (22.90)	51.97 (26.33)	49.71 (24.30)	65.55 (19.91)	59.29 (26.27)
Pizza_3	49.48 (22.77)	50.16 (19.68)	50.55 (24.72)	49.48 (22.77)	59.97 (19.59)	53.61 (23.34)
Pizza_4	53.71 (19.28)	54.48 (21.40)	53.97 (26.36)	53.71 (19.28)	59.35 (15.60)	59.29 (21.21)
Calculator	**43.69 (16.17)**	**37 (16.18)**	**44.39 (19.58)**	**43.69 (16.17)**	**49.73 (13.58)**	**55.73 (20.35)**
Calculator_1	42.03 (20.82)	31.97 (17.55)	44 (23.49)	42.03 (20.82)	48.71 (14.18)	54.52 (22.16)
Calculator_2	45.39 (23.03)	39.77 (22.06)	46.35 (23.95)	45.39 (23.03)	50.94 (20.99)	58.58 (23.90)
Calculator_3	47 (18.51)	37.84 (20.82)	46.32 (21.75)	47 (18.51)	53.77 (16.64)	56.42 (26.13)
Calculator _4	40.35 (18.65)	38.42 (18.05)	40.87 (22.49)	40.35 (18.65)	45.52 (15.64)	53.42 (22.19)
Folder	**47.64 (14.77)**	**39.1 (18.50)**	**47.7 (22.47)**	**47.64 (14.77)**	**66.45 (15.00)**	**56.58 (23.11)**
Folder_1	45.68 (17.13)	35.87 (19.03)	45.84 (25.85)	45.68 (17.13)	64.71 (19.20)	56.55 (24.34)
Folder_2	50.48 (19.78)	42.06 (25.10)	47.58 (24.67)	50.48 (19.78)	69.61 (13.28)	56.06 (27.48)
Folder_3	47.03 (19.59)	39.1 (20.56)	46.77 (25.81)	47.03 (19.59)	64.97 (21.75)	56.77 (25.71)
Folder_4	47.35 (20.26)	39.39 (21.63)	50.61 (24.27)	47.35 (20.26)	66.52 (18.68)	56.94 (22.28)
Hole-puncher	**41.07 (15.65)**	**36.02 (18.07)**	**42.33 (20.12)**	**41.07 (15.65)**	**57.98 (14.86)**	**56.62 (21.62)**
Hole-puncher_1	40 (19.91)	34.45 (19.74)	39.45 (22.21)	40 (19.91)	57.87 (18.97)	56.35 (23.96)
Hole-puncher_2	41.94 (21.03)	38.74 (20.62)	43.06 (23.58)	41.94 (21.03)	54.97 (18.45)	58.74 (25.30)
Hole_puncher_3	43.16 (17.45)	36.55 (20.14)	44.74 (22.61)	43.16 (17.45)	60.16 (18.63)	53.68 (22.08)
Hole_puncher_4	39.19 (21.12)	34.35 (18.54)	42.06 (20.83)	39.19 (21.12)	58.94 (16.20)	57.71 (23.01)
Stapler	**46.26 (15.93)**	**37.47 (17.89)**	**44.23 (20.05)**	**46.26 (15.93)**	**46.6 (13.54)**	**55.24 (22.20)**
Stapler_1	49.23 (18.36)	38.77 (20.08)	45.74 (21.65)	49.23 (18.36)	46.48 (15.90)	57.55 (24.26)
Stapler_2	46 (16.12)	37.58 (17.93)	44.19 (21.37)	46 (16.12)	47.42 (15.29)	55.23 (23.66)
Stapler_3	45.55 (22.39)	35.48 (21.22)	43.23 (23.04)	45.55 (22.39)	45.84 (15.70)	51.45 (24.48)
Stapler_4	44.26 (18.58)	38.03 (19.55)	43.74 (23.31)	44.26 (18.58)	46.68 (19.01)	56.74 (22.16)

Note. Ratings on fotorealistic stimuli were reported on a visual analogue scale ranging from 0 to 100. 100 is reflecting a high score on the corresponding scale, whereas 0 is reflecting a low score. Mean ratings and standard deviations per category and per item are reported

Table 3

Reaction times without standardization

	Mean RT Balls (SD)		**Mean RT Food (SD)**		**Mean RT Office tools (SD)**	
	T0	**T1**	**T0**	**T1**	**T0**	**T1**
Movement onset	610.15 (145.40)	570.77 (122.41)	661.02 (147.31)	625.08 (121.80)	691.54 (151.12)	649.99 (132.17)
Collection time	964.12 (478.13)	865.51 (309.86)	1054.15 (519.51)	926.28 (378.98)	1000.91 (423.81)	881.17 (296.06)

Note. The table depicts raw mean reaction times and standard deviations of the movement onset and collection time for each stimulus category (Balls, Food, Office tools) dependent on the measurement time (T0, T1).