Aus dem Institut für Medizinische Psychologie
Institut der Universität München
Vorstand: Prof. Martha Merrow, PhD

Untersuchungen des Chronotyps, des Sozialen Jetlags und der Zusammenhänge zu Nikotinkonsum

Dissertation
zum Erwerb des Doktorgrades der Medizin
an der Medizinischen Fakultät
der Ludwig-Maximilians-Universität zu München

vorgelegt von

Neda Ghotbi

aus

München

Jahr

2024

Mit Genehmigung der Medizinischen Fakultät
der Universität München

Berichterstatter:	Prof. Dr. Till Roenneberg
Mitberichterstatter:	Prof. Dr. Oliver Pogarell Prof. Dr. Jan Rémi Prof. Dr. Christoph Scheiermann
Dekan:	Prof. Dr. med. Thomas Gudermann
Tag der mündlichen Prüfung:	11.01.2024

Eidesstattliche Versicherung

Ghotbi, Neda

Name, Vorname

Ich erkläre hiermit an Eides statt, dass ich die vorliegende Dissertation mit dem Thema

Untersuchungen des Chronotyps, des Sozialen Jetlags und der Zusammenhänge zu Nikotinkonsum

selbständig verfasst, mich außer der angegebenen keiner weiteren Hilfsmittel bedient und alle Erkenntnisse, die aus dem Schrifttum ganz oder annähernd übernommen sind, als solche kenntlich gemacht und nach ihrer Herkunft unter Bezeichnung der Fundstelle einzeln nachgewiesen habe.

Ich erkläre des Weiteren, dass die hier vorgelegte Dissertation nicht in gleicher oder in ähnlicher Form bei einer anderen Stelle zur Erlangung eines akademischen Grades eingereicht wurde.

München, 12.01.2024

Ort, Datum

Neda Ghotbi

Unterschrift Neda Ghotbi

Inhaltsverzeichnis

Publikationsliste

Arbeiten, die Bestandteil der genannten kumulativen Dissertation sind:

1. **Ghotbi, N**., Pilz, L.K., Winnebeck, E.C., Vetter, C., Zerbini, G., Lenssen, D., Frighetto, G., Salamanca, M., Costa, R., Montagnese, S., Roenneberg, T., 2020. The µMCTQ: An Ultra-Short Version of the Munich ChronoType Questionnaire. Journal of Biological Rhythms 35, 98–110. https://doi.org/10.1177/0748730419886986

2. **Ghotbi N**, Rabenstein A, Pilz LK, Rüther T, Roenneberg T. Chronotype, Social Jetlag, and Nicotine Use. Journal of Biological Rhythms. 2023;38(4):392-406. doi:10.1177/07487304231177197

Sonstige Arbeiten (nicht zur kumulativen Dissertation eingereicht):

3. Loock, A.-S., Khan Sullivan, A., Reis, C., Paiva, T., **Ghotbi, N**., Pilz, L.K., Biller, A.M., Molenda, C., Vuori-Brodowski, M.T., Roenneberg, T., Winnebeck, E.C., 2021. Validation of the Munich Actimetry Sleep Detection Algorithm for estimating sleep–wake patterns from activity recordings. Journal of Sleep Research 30, e13371. https://doi.org/10.1111/jsr.13371

1. Eigener Beitrag zu den Veröffentlichungen

1.1 Eigener Beitrag zu Paper I (Validierung des µMCTQ)

Bei dieser Forschungsarbeit handelte es sich um die Konzeption und Untersuchung der Validität und Reliabilität eines neuen Kurz-Fragebogens zur Erfassung des Chronotypen und des Sozialen Jetlags, genannt „micro Munich ChronoType Questionnaire“ (kurz: µMCTQ). Ein bereits vorhandener Fragebogen (Langversion des µMCTQ, der Munich ChronoType Questionnaire, kurz: MCTQ) wurde ebenfalls auf seine Validität in dieser Forschungsarbeit untersucht bzw. bereits vorhandene Ergebnisse konnten repliziert werden. Durch den µMCTQ generierte Daten wurden in dieser Arbeit mit Daten anderer etablierter chronobiologischer Messmethoden verglichen. Verglichen wurde der µMCTQ mit Aktivitätsdaten (Aktimetrie), Melatonin-Messungen im Speichel und dem MCTQ. Die Studie erfolgte in Kooperation mit der Universität Padova, weswegen ein Teil der (Fragebogen-)Daten aus einer italienischen Kohorte stammte.

Ich trug zu der genannten Forschungsarbeit bei, indem ich an der Konzeption des Studiendesigns mitarbeitete und hierzu vorab ausführliche (Literatur-)Recherchen zum aktuellen Forschungsstand und zu Durchführungsmöglichkeiten vornahm, sowie statistische Power-Analysen zur Anzahl der Proband:innen vorab durchführte. Ebenso verfasste ich den Ethikantrag und reichte diesen, nach Revision durch meinen Doktorvater, ein. Ausbesserungen basierend auf Vorschlägen der Ethikkommission nahm ich ebenfalls vor. Anschließend führte ich die Studie am Münchner Standort gemeinsam mit dem Studienteam durch. Ich konzipierte gemeinsam mit Frau Pilz eine online-Version des Fragebogens und testete diese vor Studienbeginn. Ich rekrutierte Proband:innen in München und sammelte deren Daten online sowie in Person. Die Rekrutierung erfolgte durch Aufrufe im Institut für Medizinische Psychologie, die Nutzung des LMU-Newsletters und anschließend telefonische oder persönliche Studienaufklärung bzw. Prüfung der Ein- und Ausschlusskriterien. Die Datensammlung erfolgte durch die Beantwortung des online-Fragebogens, kontinuierlich über Aktivitätsmesser (sog. Aktimeter), Speichelprobensammlung und durch Fragebögen und Schlafprotokolle in Papierform. Ich führte eine ausführliche Instruktion der Proband:innen zur Benutzung der Aktimeter sowie der Gewinnung der Speichelproben

(mehrere Messungen über einige Stunden) durch. Anschließend war ich mit der Aufbereitung und Eingabe des gesamten Datensatzes (Fragebögen, Auslesen der Aktivitätsmessungen/Aktimetrie) und der Speichelproben (*dry* und *wet lab* Arbeit) betraut, um diese auswerten zu können. Die Speichelproben bereitete ich im Labor für anschließende Radioimmunoassays vor, indem ich die Proben bearbeitete, katalogisierte, fachgerecht lagerte und Probenduplikate hinterlegte. Ich wertete den vollständigen Datensatz (aus Padova und München) hinsichtlich demographisch-deskriptiver Aspekte aus, berechnete Schlüsselvariablen zur Ermittlung des Chronotypen und des sozialen Jetlags, ebenso führte ich gemeinsam mit Frau Pilz Korrespondenz- (Bland-Altmann Analysen), Korrelations- und Reliabilitätsanalysen hinsichtlich der unterschiedlichen erhobenen Variablen durch. Die Radioimmunoassays erfolgten in einem anderen spezialisierten Labor. Für diese Kooperation war ich ebenfalls verantwortlich und wickelte den Prozess ab (Probenvorbereitung, -transport, Kommunikation). Nach erfolgter Datenanalyse, erstellte ich die Erstfassung des Manuskripts und arbeitete sukzessive Rückmeldungen der anderen Ko-Autor:innen ein. Ich reichte das Manuskript beim *Journal of Biological Rhythms* ein und nahm Anpassungen, entsprechend der Vorschläge der Peer-Review, vor.

Die geteilte Erstautorenschaft kam zustande, da sowohl Frau Pilz als auch ich zu gleichen Teilen an der Datenanalyse (s.o.) beteiligt waren. Ebenso rekrutierten wir gemeinsam Proband:innen und an der Recherche vor Studienbeginn sowie den abschließenden Revisionen des Manuskripts war sie ebenfalls beteiligt.

1.2 Eigener Beitrag zu Paper II (Zusammenhang Nikotinkonsum und circadiane Uhr)

Bei dieser Forschungsarbeit handelte es sich um die Untersuchung des Einflusses von Nikotinkonsum auf die circadiane Uhr des Menschen. Hierzu wurden Messungen vor und nach Rauchstopp miteinander verglichen und besonderes Augenmerk wurde auf potenzielle Veränderungen beim Chronotyp und beim Sozialen Jetlag gelegt. Schlafqualitative Erhebungen (Fragebögen) erfolgten neben demographischer Datenerhebung ebenfalls. Es erfolgten Aktivitätsmessungen, Melatonin-Messungen im Speichel und der MCTQ wurde eingesetzt. Es wurde der Fragestellung nachgegangen, ob Rauchen zu einem späteren Chronotyp führt, und so zu mehr sozialem Jetlag, oder ob Rauchen als Strategie im Umgang mit sozialem Jetlag eingesetzt wird.

Ich trug zu dieser Forschungsarbeit bei, indem ich von Beginn an, an der Konzeption des Studiendesigns mitarbeitete und hierzu ausführliche (Literatur-)Recherchen zum aktuellen Forschungsstand sowie zu Durchführungsmöglichkeiten vornahm. Ich nahm im Zuge der vorausgehenden Planung Kontakt zur Tabakambulanz der Klinik für Psychiatrie und Psychotherapie auf und bahnte die Projekt-Kooperation. Ich verfasste den Ethikantrag und reichte diesen nach Revision durch meinen Doktorvater bei der Ethikkommission ein. Ausbesserungen, basierend auf Vorschlägen der Ethikkommission, nahm ich ebenfalls vor. Ich führte die Studie durch, indem ich Proband:innen über verschiedene Kanäle (Zeitungsannoncen, Newsletter der Universität) rekrutierte und über die Studienteilnahme vorab telefonisch aufklärte bzw. die Ein- und Ausschlusskriterien prüfte. Ich führte, jeweils mit wechselnden Ko-Leitungen, wiederholt mehrwöchige (9 Termine/Wochen pro Kurs) Rauchentwöhnungskurse nach etablierten verhaltenstherapeutischen Manualen in der psychiatrischen Klinik durch. So sammelte ich fortlaufend, über die Dauer mehrerer Monate, Daten aus Fragebögen, Aktivitätsmessungen und Speichelproben. Ebenso führte ich zu jedem Termin Messungen des Kohlenstoffmonoxidgehalts der Umgebungs- und Atemluft der Proband:innen durch. Im Anschluss bereitete ich die Daten auf (in Vorbereitung zur Datenanalyse, *dry* und *wet lab* Arbeit) in dem ich die Dateneingabe durchführte, Aktivitätsdaten auslas und die Speichelproben für anschließende ELISA-Untersuchungen aufbereitete bzw. Probenduplikate anfertigte, katalogisierte und lagerte. Zur anschließenden Auswertung untersuchte ich den umfangreichen Datensatz hinsichtlich deskriptiv-demographischer Informationen und errechnete Schlüsselvariablen aus Fragebogen- und Aktivitätsmessungsdaten. Ich berechnete anschließend statistische Modelle zur Beantwortung der oben genannten Fragestellung. Hierzu berechnete ich verallgemeinerte Schätzgleichungen, binäre logistische Regressionen, nicht-parametrische Tests und Korrelationsanalysen. Ich erstellte anschließend das Manuskript, was ich in Rücksprache mit den Ko-Autor:innen fortlaufend anpasste. Ich reichte das Manuskript zur Veröffentlichung beim *Journal of Biological Rhythms* ein und nahm die gewünschten Anpassungen der Peer-Review, in Rücksprache mit den Ko-Autor:innen, vor.

Bei dieser Arbeit liegt keine geteilte Erstautorenschaft vor.

2. Einleitung

2.1 Allgemeine Einleitung

2.1.1 Das biologische Programm der circadianen Uhr

Die „circadiane Uhr“ ist ein biologisches Programm, das der Synchronisierung des individuellen Organismus mit der zyklisch organisierten Umwelt dient. Hierbei synchronisiert sich die circadiane Uhr aktiv mit spezifischen Umweltsignalen – sogenannten *zeitgebern*. Für Menschen, sowie für die meisten anderen Organismen, ist Licht das wichtigste Umweltsignal (Duffy and Wright, 2005; Roenneberg et al., 2007b; Wright et al., 2013). Durch Photorezeptoren der Retina wird das Lichtsignal in den suprachiasmatischen Nucleus (kurz: SCN) geleitet, der die zentrale Organisationseinheit der circadianen Uhr bildet und auch periphere Oszillatoren (auf zellulärer Ebene und in anderen Geweben wie z.B. der Leber) mitreguliert (Ko and Takahashi, 2006). Für den gesamten Organismus entsteht eine individuelle Phasenbeziehung zwischen dem zeitgeber und der circadianen Uhr. Diese kann zum Beispiel mittels des Tiefpunktes der Körperkerntemperatur, Schlafzeitpunkte oder des Beginns der Melatonin-Ausschüttung am Abend referenziert werden (Klerman et al., 2022; Roenneberg et al., 2007b, 2003a).

2.1.2 Chronotyp

Die individuelle Phasenbeziehung der circadianen Uhr zum zeitgeber, wird beim Menschen häufig auch als „Chronotyp“ bezeichnet. Dieser variiert individuell, aufgrund genetischer Varianz (sog. *clock genes*), und bedingungsabhängig (Roenneberg, 2012; Roenneberg et al., 2007a). In der Bevölkerung ist er annähernd normalverteilt und seine Verteilung reicht von extrem frühen Chronotypen (umgangssprachlich „Lerchen“ genannt) zu extrem späten Chronotypen (umgangssprachlich „Eulen“) (Roenneberg et al., 2007a). Die meisten physiologischen Prozesse sind zeitlich in Bezug zum Chronotypen organisiert, so auch die Schlafzeiten (Roenneberg et al., 2003a).

Der Chronotyp wird in der Forschungsliteratur mitunter als psychologisches Merkmal (engl.: *trait*) diskutiert, welches unabhängig von bedingenden situativen Umweltfaktoren besteht (Horne and Ostberg, 1976; Steyer et al., 1992). Die circadiane Uhr des

Menschen ist jedoch stetig mit wechselnden Umweltbedingungen und zeitgebern konfrontiert. Hierbei gelingt es ihr sich anzupassen bzw. sich zu synchronisieren und sie weist somit durchaus situativ variierende Aspekte auf (engl.: *state*). In der Folge kann der Chronotyp also als biologische *state-trait*-Interaktion gesehen werden, die die zeitliche Strukturierung und Organisation des gesamten Organismus widerspiegelt. Die Varianz der Umweltbedingungen, genetischer Faktoren und die Altersentwicklung, tragen gemeinsam zur Varianz des Chronotypen bei (Roenneberg et al., 2019).

2.1.3 Sozialer Jetlag

Durch den modernen Lebensstil, entsteht meist eine geringe Exposition mit natürlichem Licht am Tag (z.B., Leben und Arbeiten in Gebäuden/geschlossenen Räumen) und ein Mangel an Dunkelheit am Abend (z.B., Nutzung von künstlichem Licht) (Roenneberg et al., 2019, 2003a; Stothard et al., 2017). Diese Prozesse stellen eine Herausforderung für die Synchronisierung von Innen- und Außenzeit dar, da die Stärke des zeitgebers Licht stark eingeschränkt wird, viele Chronotypen später werden und sich die Schere bzw. Verteilung zwischen späten und frühen Chronotypen weitet (Porcheret et al., 2018; Wright et al., 2013). Nachdem sich aber die meisten sozial bzw. gesellschaftlich vorgegebenen Zeiten (wie z.B. Schul- oder Arbeitsbeginn) nicht entsprechend angepasst haben, entsteht eine zunehmende Diskrepanz zwischen der Innen- und der Außenzeit, der sog. *soziale Jetlag*, der auch beispielsweise darin Ausdruck findet, dass die meisten Menschen einen Wecker an Arbeitstagen nutzen (Wittmann et al., 2006). Diese Diskrepanz führt unter anderem zu über die Arbeitswoche akkumulierendem Schlafmangel, der häufig an freien Tagen, durch längeres Schlafen, kompensiert wird (Wittmann et al., 2006).

Zahlreiche Gesundheitsrisiken sind mit dem Vorliegen von chronischem sozialen Jetlag assoziiert: darunter fallen erhöhte Risiken für die Entstehung von psychischen Erkrankungen, wie Depressionen oder Suchterkrankungen, ebenso entstehen Risiken für die Entwicklung von Stoffwechselerkrankungen wie Diabetes oder Übergewicht oder für kardiovaskuläre Ereignisse (Antypa et al., 2016; Broms et al., 2012; Levandovski et al., 2011; Parsons et al., 2015; Roenneberg et al., 2012; Wong et al., 2015).

2.2 Einleitung Forschungskontext µMCTQ: Messmethoden in der Chronobiologie

Verschiedene Messmethoden zur Untersuchung der circadianen Uhr bzw. „Chronotypisierung“ liegen vor. Beim Menschen kommen hormonelle Messungen, Aktivitätsmessungen und Evaluationen durch Fragebögen beispielsweise in Frage und sollen im Folgenden erläutert werden (Klerman et al., 2022).

2.2.1 Melatonin Messung

Das zeitliche Profil der (abendlichen) Melatonin-Ausschüttung (engl.: dim light melatonin onset, kurz: DLMO), stellt die Goldstandardmethode zur Erfassung der Phase der circadianen Uhr dar (Benloucif et al., 2008; Klerman et al., 2002; Lewy and Sack, 1989). Melatonin ist ein schlafanstoßendes Hormon, welches in der Glandula pinealis bzw. der Epiphyse gebildet wird (Arendt, 2006). Blauwelliges Licht am Abend unterdrückt die Melatonin-Ausschüttung, während Melatonin bei Dunkelheit oder Dämmerung wirksam ausgeschüttet wird (Arendt and Skene, 2005). Die Melatonin-Ausschüttung korreliert mit zunehmender Schläfrigkeit und einer sinkenden Körperkerntemperatur (Arendt and Skene, 2005). Ebenso sind Korrelationen zur Aktivitätsmessungen und Erfassungen des Chronotypen mittels Fragebögen gefunden worden (Ghotbi et al., 2020; Kantermann et al., 2015). Melatonin und dessen Ausschüttungsprofile können (beim Menschen) im Speichel, Blutserum oder Urin bestimmt werden (De Almeida et al., 2011). Hierbei sind mehrfache, abendliche Probengewinnungen unter standardisierten Bedingungen notwendig (z.B. Tragen von Brillen, die blauwelliges Licht filtern oder Einhaltung bestimmter Zeitabstände) um individuelle Phasenprofile erstellen zu können (Klerman et al., 2022, 2002).

2.2.2 Aktivitätsmessungen (Aktimetrie)

Aktivitätsmessungen können mit dem sogenannten Aktimeter durchgeführt werden. Das Aktimeter ist ein Messgerät, das am Handgelenk getragen wird und durch ein eingebautes Akzelerometer lokomotorische Aktivität erfasst und diese Daten speichert (Roenneberg et al., 2015). Zur Auswertung können spezialisierte Software-Algorithmen/Berechnungsmethoden angewendet werden, die Phasen von Aktivität und Inaktivität unterscheiden können (Roenneberg et al., 2015). So ist es beispielsweise möglich die Akrophase der Aktivität zu errechnen, also den maximalen Punkt der Aktivität innerhalb einer Aufbereitung der Aktivitätsdaten entlang einer angepassten 24-

Stunden Cosinus-Kurve (das Aktimeter erfasst lediglich Ereignisse, die entlang ihres zeitlichen Auftretens aufbereitet werden). Dieser kann auch als zeitlicher „Aktivitätsschwerpunkt“ definiert werden (Ghotbi et al., 2020; Loock et al., 2021). Dieser „Aktivitätsschwerpunkt“ kann als Näherungsvariable für den Chronotyp verwendet werden, da gezeigt werden konnte, dass er mit anderen Messmethoden gut korreliert (Ghotbi et al., 2020).

2.2.3 Fragebögen: MEQ und MCTQ

Zur Erfassung des Chronotypen stehen im Wesentlichen zwei etablierte Fragebogenverfahren zur Verfügung. Das zentrale Unterscheidungsmerkmal der Verfahren ist das zugrundeliegende Konzept des Chronotypen. Der sogenannte Morningness-Eveningness Fragebogen, kurz MEQ, evaluiert den Chronotyp im Sinne eines psychologischen Konstruktes oder *trait* (siehe oben). Hierzu werden die tageszeitlichen Präferenzen für bestimmte Handlungen oder Aktivitäten erhoben. Anhand einer insgesamt errechneten Summenpunktezahl erfolgt schließlich die Einteilung in „Früh-Typen“, „Intermediäre Typen“ und „Abend-Typen“, entlang der zeitlichen Präferenzangaben (Horne and Ostberg, 1976). Der MCTQ hingegen evaluiert den Chronotyp als biologisches Konstrukt, im Sinne einer *state-trait*-Interaktion (siehe oben). Hierbei spielen also weniger zeitliche Präferenzen und mehr die quantifizierbaren Zeitpunkte für Schlaf und Wachheit die zentrale Rolle (Roenneberg et al., 2019). Sie werden getrennt für freie und Arbeitstage erhoben. Schlafzeitpunkte an freien Tagen werden zur Typisierung schließlich verwendet, da davon auszugehen ist, dass freie Tage repräsentativer für die Synchronisierungsphase der circadianen Uhr sind, nachdem weniger äußere Einflussfaktoren das Schlaf-Wach-Verhalten beeinflussen (Roenneberg et al., 2003b). Der Chronotyp ist im MCTQ als der Mittelzeitpunkt des Schlafes an freien Tagen definiert, der für ausgleichende Schlafkompensation zusätzlich korrigiert wird (Roenneberg et al., 2003b). Durch die Berechnung der Variablen separat an freien und an Arbeitstagen, ist die Feststellung von Diskrepanzen, bzw. von sozialem Jetlag, möglich (Wittmann et al., 2006).

2.3 Projekt 1: µMCTQ Validierung

2.3.1 Darstellung Forschungsarbeit: µMCTQ Validierung

Nachdem die circadiane Uhr auf die meisten Funktionen des menschlichen Körpers direkte oder indirekte Einflüsse ausübt (Roenneberg et al., 2022) und die beschriebenen Diskrepanzen zwischen Innen- und Außenzeiten für den Organismus problematisch sein können, ist eine möglichst genaue Kenntnis über diese Prozesse über ein breites Spektrum von Bedingungen für chronobiologische Forschung und z.B. die Translation in circadiane Medizin erstrebenswert (Baron and Reid, 2014; Beauvalet et al., 2017; Klerman et al., 2022; Knutson and von Schantz, 2018; Wittmann et al., 2006). Dafür ist eine möglichst genaue Bestimmung der Phase der Synchronisierung, also, des Chronotypen essentiell (Roenneberg, 2012). Es bestehen Goldstandard-Methoden den Chronotypen über den Zeitpunkt des Beginns der Melatonin-Ausschüttung bzw. dessen Ausschüttungsprofils (engl.: *dim light melatonin onset*, kurz: DLMO), zu ermitteln. Hierzu sind bisweilen Speichel-, Blut- oder Urinproben notwendig (Benloucif et al., 2008; Klerman et al., 2002; Lewy and Sack, 1989). Diese Messungen sind allerdings teuer und sehr aufwändig, da sie hohe Anforderungen an die Proband:innen für eine korrekte zeitliche und methodische Durchführung stellen. Denn zur korrekten DLMO-Bestimmung ist die Gewinnung mehrerer Proben über den Zeitraum einiger Stunden und unter Einhaltung zahlreicher Bedingungen notwendig (Einhaltung von Abständen zur Einnahme von Nahrungsmitteln und Getränken, Vermeidung von blauwelligem Licht, etc.) (Braun et al., 2018; Wittenbrink et al., 2018). Daher erscheint es wichtig eine kostengünstige, nicht-invasive, und einfach umsetzbare Methode zur Ermittlung des Chronotypen zu entwickeln, um ausreichend große Datenmengen über verschiedene Kontexte/Bedingungen zeiteffizient generieren zu können. Der Munich Chronotype Questionnaire (kurz: MCTQ) nutzt den Zeitpunkt des Schlafes zur Chronotyp-Ermittlung. Hierbei werden Schlafzeitpunkte separat für freie und Arbeitstage ermittelt und der Chronotyp durch die Mittelzeitpunktes des Schlafes an freien Tagen, korrigiert für Schlafkompensation, definiert. Freie Tage werden gewählt, da davon auszugehen ist, dass diese weniger durch sozial/gesellschaftlich vorgegebene Zeiten bestimmt sind, als Arbeits-/Schultage (Roenneberg et al., 2003b). Der Fragebogen wurde in mehreren Studien bereits validiert (Kantermann et al., 2015; Kitamura et al., 2014; Wright et al., 2013).

In dieser Studie wurde nun eine verkürzte Version des MCTQ generiert: der micro MCTQ oder µMCTQ, der sich auf die zentralen Chronotyp-Module der Langfassung konzentriert. So stellt der µMCTQ eine einfach umsetzbare, nicht-invasive und zeiteffiziente Messmethode zur Chronotyp-Ermittlung dar (Ghotbi et al., 2020). In der Proband:innen-Gruppe, wurden Parameter, die durch den µMCTQ erhoben worden sind, mit MCTQ Messparametern, DLMO und Aktivitätsmessungen (Aktimetrie), verglichen. Der Fragebogen wurde hinsichtlich seiner Validität und Reliabilität untersucht. Die Datensätze stammten zu Teilen aus Italien (Universität Padua) und zu Teilen aus Deutschland (LMU München) (Ghotbi et al., 2020).

2.3.2 Ergebnisse der Forschungsarbeit: µMCTQ Validierung

Die Studie hatte zum Ergebnis, dass der µMCTQ eine gute Validität und Reliabilität hinsichtlich der Chronotyp-Ermittlung, im Vergleich zu anderen objektiven Standardmethoden (DLMO, Aktimetrie), aufwies (Ghotbi et al., 2020). Ebenso konnten Ergebnisse der guten Validität des MCTQ repliziert werden (Ghotbi et al., 2020). Zusammenfassend stellt der µMCTQ eine valide und auch in größeren Studien gut nutzbare und kompakte Messmethode zur Erhebung relevanter Parameter der circadianen Uhr des Menschen dar (Ghotbi et al., 2020).

2.4 Einleitung Forschungskontext Nikotinkonsum und circadiane Uhr

Laut Auswertungen der Weltgesundheitsorganisation (WHO) werden, trotz des auf globalem Niveau sinkenden Tabakkonsums, im Jahr 2025 weiterhin circa 17,1 % der Weltbevölkerung rauchen. Ebenso wird die Zahl der Todesfälle, die durch Tabakkonsum vermittelt ist, weiter ansteigen (World Health Organization, 2019). Rauchen stellt weiterhin eine der größten vermeidbaren Krankheits- bzw. Todesursachen in der Welt dar (Samet, 2013). Somit ist es äußerst relevant das Wissen, hinsichtlich der Effekte von Tabakkonsum und zu berücksichtigender Faktoren für eine erfolgreiche Rauchentwöhnung bzw. Tabakprävention, zu erweitern. Im Folgenden wird der bereits festgestellte Zusammenhang zwischen sozialem Jetlag und einer erhöhten Prävalenz von Nikotinkonsum näher erläutert. Hierzu wird zunächst auf allgemeine motivierende Faktoren für das Rauchen eingegangen, bevor der Zusammenhang zu sozialem Jetlag genauer beleuchtet wird.

2.4.1 Motivatoren für Nikotin- und Tabakkonsum

Viele motivierende Faktoren für den Beginn und die Aufrechterhaltung von Nikotinkonsum sind in der Literatur bereits beschrieben worden. Darunter fallen beispielsweise die Modulation kortikaler Erregung zur Konzentrationsförderung und Steigerung der Verarbeitungsgeschwindigkeit oder Emotionsregulation (zum Beispiel zur Bewältigung emotionaler Belastungszustände) (Ernst et al., 2001; Heishman et al., 2010; Kassel et al., 2003; Lujic et al., 2005). Ebenso sind subjektiv empfundener Stress- und Anspannungsabbau häufig beschriebene Zwecke zu denen Rauchen eingesetzt wird (Fidler and West, 2009; West et al., 2005). In der Forschungsliteratur hierzu wird vielfach diskutiert ob diese Motivatoren tatsächliche Verbesserungen der kognitiven Fertigkeiten oder des Stressniveaus mit sich bringen oder ob es sich bei den empfundenen Effekten vielmehr um die Unterdrückung von Entzugssymptomen handelt, die dann wiederum die Beibehaltung von Rauchen fördern (Parrott, 1995, 1994; West, 1993). In einer von Heishman et al. veröffentlichten Meta-Analyse hingegen, wird über zunehmende (qualitative und quantitative) Evidenz berichtet, die für tatsächliche Verbesserungen in den genannten Teilbereichen, vermittelt durch Tabak- und Nikotinkonsum, spricht – dies legt also nahe zumindest nicht ausschließlich von der Unterbindung von Entzugssymptomen auszugehen (Heishman et al., 2010). In Zusammenschau der hinzugezogenen Fachliteratur, erscheint es aktuell schwer möglich von Korrelationen kausale Zusammenhängen abzuleiten, da die zugrundeliegenden Mechanismen nach wie vor kontrovers diskutiert werden (Kassel et al., 2003; West, 1993). Über die Kausalitäten scheinen noch große Unklarheiten zu bestehen und die Unterdrückung von Entzugssymptomen könnte somit ein potenziell ubiquitär auftretender Störfaktor innerhalb der Ermittlung der Motivatoren (für Tabakkonsum) sein. Nichtsdestotrotz ist es möglich, dass Raucher:innen, unabhängig der tatsächlich nachweisbaren Effekte und Gründe, Rauchen subjektiv als Bewältigungsstrategie verwenden. Es konnte nämlich gezeigt werden, dass Raucher:innen dem Rauchen genau diese genannten positiven Effekte zuschreiben und sich diese vom Rauchen auch erwarten (Baker et al., 2004; Brandon et al., 1999; Copeland et al., 1995; Wetter et al., 1994).

2.4.2 Zusammenhänge zwischen Sozialem Jetlag und Rauchen

Belastungen der circadianen Uhr, wie zum Beispiel vorliegender sozialer Jetlag, tragen wahrscheinlich zu subjektiv empfundenem Stress oder geringerer Wachheit bei

(McEwen and Karatsoreos, 2015; Okajima et al., 2021; Tamura et al., 2022). Nachdem für Rauchen und sozialen Jetlag eine starke Assoziation beschrieben worden ist, ist es möglich, dass Rauchen als Linderung dieser negativen Effekte von sozialem Jetlag genutzt wird – zusätzlich zur Unterdrückung von Entzugssymptomen und/oder anderen motivierenden Faktoren (s.o.) (Wittmann et al., 2006).

Sozialer Jetlag zeigt einige negative gesundheitliche Auswirkungen. So ist beispielsweise ein Zusammenhang zu depressiven Symptomen beschrieben worden (Levandovski et al., 2011). Geringere Leistungsfähigkeit (schulisch oder am Arbeitsplatz), (McGowan et al., 2020; Yong et al., 2016), ein höheres kardiovaskuläres Risiko oder ein erhöhtes Risiko für Stoffwechselerkrankungen ist ebenfalls bereits berichtet worden (Koopman et al., 2017; Parsons et al., 2015; Wong et al., 2015). Wittmann et al. haben zusätzlich argumentiert, dass späte Chronotypen, die in der Konsequenz unter mehr sozialem Jetlag leiden, und die rauchen und Alkohol trinken, mehr psychische Belastungen sowie insgesamt ein geringeres psychisches Wohlbefinden berichten, als späte Chronotypen, die kein solches Konsumverhalten zeigen (Wittmann et al., 2010). So ziehen Wittman et al. den Schluss, dass der Substanzgebrauch die psychische Belastung vermittelt, was die Hypothese bestärkt, dass durch Substanzgebrauch additiv negative Effekte zu sozialem Jetlag entstehen (Wittmann et al., 2010). Weitere Arbeiten beschreiben ein höheres Risiko für die Entwicklung von Abhängigkeiten bei vorliegendem sozialem Jetlag (Logan et al., 2018) und höhere Wahrscheinlichkeiten für schädlichen Alkoholkonsum sind ebenfalls beschrieben worden (Borisenkov et al., 2019; Haynie et al., 2018). Höhere Kortisol-Spiegel (hinweisend auf die Aktivierung der sogenannten Stress-Achse) bei sozialem Jetlag und erhöhte Tagesmüdigkeit konnten ebenfalls in verschiedenen Forschungsarbeiten festgestellt werden (Choi et al., 2019; Komada et al., 2016; Rutters et al., 2014).

Es ist also denkbar, dass eine Kombination der genannten Effekte von sozialem Jetlag, wie beispielsweise höherer subjektiver Stress, Tagesmüdigkeit oder gedrückte Stimmung, einen Beitrag zum Beginn und zur Aufrechterhaltung von Tabakkonsum leisten, insbesondere wenn gemeinhin die Erwartung besteht, dass Rauchen in diesen Situationen hilfreich sein kann (Baker et al., 2004; Brandon et al., 1999; Copeland et al., 1995; Wetter et al., 1994).

Hinsichtlich des Zusammenhangs von sozialem Jetlag und Rauchen ist weiterhin hervorzuheben, dass meistens während der Adoleszenz mit dem Rauchen begonnen wird

(DHHS, 2014; Wellman et al., 2016). Interessanterweise sind bei Jugendlichen zwar auch die oben genannten Motivatoren vertreten, jedoch spielen psychosoziale Faktoren in dieser Kohorte eine deutlich größere Rolle als in älteren Gruppen (Kobus, 2003; Lujic et al., 2005). Aus der chronobiologischen Perspektive, ist die Adoleszenz die Entwicklungsphase, innerhalb derer die circadiane Uhr des Menschen dem größten Druck ausgesetzt ist (Gradisar et al., 2022). In der Entwicklungsphase der Adoleszenz, wird der Chronotyp kontinuierlich später (im Vergleich zum Kindesalter) und erreicht seinen spätesten Punkt zwischen 19 – 21 Jahren, bevor er ab dann wieder beginnt früher zu werden (Roenneberg et al., 2007a). Während Jugendliche also recht frühe gesellschaftlich determinierte Zeiten berücksichtigen müssen (z.B. Schul- oder Ausbildungsbeginn), ist die innere Uhr in dieser Gruppe relativ spät und der soziale Jetlag somit deutlich intensiviert (Roenneberg et al., 2012).

Die hohe Anzahl an beginnenden Raucher:innen in der Adoleszenz, könnte somit zum Teil damit erklärt werden, dass Rauchen als Strategie im Umgang mit den beschriebenen Belastungen von sozialem Jetlag eingesetzt wird, die in der Adoleszenz vermehrt vorkommen. Weiterhin ist es möglich, dass Individuen mit spätem Chronotyp über die Dauer ihrer Lebensspanne relativ gesehen weniger Entlastung von sozialem Jetlag erfahren werden (wenn ihre circadiane Uhr „früher“ wird), was die Beibehaltung des Tabakkonsums auch über die Adoleszenz hinaus weiter fördern könnte. Einige Studien (in Menschen und Tiermodellen) haben gezeigt, dass das jugendliche Gehirn sensitiver auf niedrige Dosen von Nikotin reagiert, als das erwachsene Gehirn (Smith et al., 2015; Trauth et al., 2001). Interessanterweise sind auch Langzeitveränderungen der neuronalen Struktur und Konnektivität des Gehirns nach Nikotinexposition beschrieben worden (Smith et al., 2015; Yuan et al., 2015). Einige Autor:innen legen auch nahe, dass epigenetische Veränderungen nach Nikotinexposition vorkommen könnten und dass diese Effekte gemeinsam zur Beibehaltung von Nikotin- bzw. Tabakkonsum, sowie zu einer erhöhten Wahrscheinlichkeit für substanzgebundene Abhängigkeiten über die Lebensspanne, beitragen könnten (Yuan et al., 2015).

2.5 Projekt 2: Nikotinkonsum und circadiane Uhr

2.5.1 Darstellung der Forschungsarbeit: Nikotinkonsum und circadiane Uhr

Die durchgeführte Studie zielte darauf ab den Zusammenhang zwischen Rauchen und der circadianen Uhr des Menschen näher zu untersuchen, da vorausgegangene Studien

eine erhöhte Prävalenz zwischen Rauchen und dem Vorliegen eines späten Chronotypen und sozialen Jetlags herausgefunden haben (Ghotbi et al., 2023; Wittmann et al., 2006). Ebenso sind Zusammenhänge zwischen schlechterer Schlafqualität und Rauchen sowie eine gestörte Schlafarchitektur bei Raucher:innen bereits beschrieben worden (Hu et al., 2007; Jaehne et al., 2012; Phillips and Danner, 1995; Wetter and Young, 1994). Somit erfolgte in dieser Studie auch eine Erfassung verschiedener Dimensionen der Schlafqualität (Ghotbi et al., 2023).

Zwar ist eine positive Korrelation zwischen sozialem Jetlag und der Wahrscheinlichkeit zu rauchen bereits beschrieben worden (Wittmann et al., 2006), unklar blieb jedoch ob Rauchen zu einem späteren Chronotyp (und somit mehr sozialem Jetlag) führt (Hypothese 1) oder ob sozialer Jetlag (welcher bei späten Chronotypen häufig vorkommt) ursächlich zum Rauchen, beispielsweise als Bewältigungsstrategie, beiträgt (Hypothese 2). Somit wurden in dieser Studie Raucher:innen durch den Prozess der verhaltenstherapeutisch unterstützten Rauchentwöhnung (ohne Nikotinersatzpräparate) begleitet und Messungen der circadianen Uhr und des Schlafes jeweils vor und nach dem Rauchstopp erhoben bzw. verglichen (Ghotbi et al., 2023). Sollte die erste Hypothese zutreffen und Rauchen zu späteren Chronotypen führen, sollte der Chronotyp nach Rauchstopp somit früher werden. Sollten sich die erhobenen Parameter jedoch nicht signifikant nach dem Rauchstopp verändern, ist die zweite Hypothese, also Rauchen als Bewältigungsstrategie bei sozialem Jetlag, wahrscheinlicher (Ghotbi et al., 2023).

2.5.2 Ergebnisse der Forschungsarbeit: Nikotinkonsum und circadiane Uhr

Die Ergebnisse der Forschungsarbeit zeigen, dass insgesamt keine statistisch signifikanten Effekte von Rauchentwöhnung auf erhobene Parameter der circadianen Uhr und des Schlaf-Wach-Rhythmus (Chronotyp, sozialer Jetlag, Aktimetrie-Messungen, Schlafqualität und Tagesmüdigkeit) festzustellen waren (Ghotbi et al., 2023). Somit erscheint die Erklärung, dass Rauchen kompensatorisch für das Vorliegen von sozialem Jetlag und einhergehender Belastungen eingesetzt wird, wahrscheinlicher zugrundeliegend für die beschriebene Assoziation zwischen Rauchen und späten Chronotypen bzw. sozialem Jetlag (Ghotbi et al., 2023).

2.6 Übergeordnete und verbindende Fragestellung der Forschungsarbeiten

Es wurde der übergeordneten Fragestellung der Untersuchung des circadianen Schlaf-Wach-Rhythmus bei Menschen und dessen Beziehung zu Nikotinkonsum nachgegangen. Hierzu wurde im ersten Schritt der Fokus auf die Untersuchungsmethodik bzw. Untersuchbarkeit der circadianen Uhr des Menschen gelegt, da die Bestimmung des Chronotypen eine wichtige Grundlage für chronobiologische Forschungsvorhaben bildet. Die Validität und Reliabilität eines nicht-invasiven und niedrigschwellig einsetzbaren Messinstruments zur Ermittlung wesentlicher Parameter, wie beispielsweise des Chronotyps oder des sozialen Jetlags, wurde untersucht. Ein kurzer und anwenderfreundlicher Fragebogen, der µMCTQ, wurde entwickelt, während die Validierung dessen Langfassung, des MCTQ, ebenfalls repliziert werden konnte (Ghotbi et al., 2020; Kantermann et al., 2015; Kitamura et al., 2014; Pilz et al., 2018). Der neu entwickelte µMCTQ stellt nun eine Möglichkeit zur vereinfachten und breit angelegten Untersuchung der circadianen Uhr des Menschen dar, welche insbesondere bei größeren Datenerhebungen von Vorteil ist (Ghotbi et al., 2020). Hiermit ermöglicht er Einblicke in die Phase der Synchronisierung (Chronotyp) und in die potenziell bestehenden Diskrepanzen zwischen Innen- und Außenzeit (sozialer Jetlag). Durch die Fokussierung auf zentrale Chronotyp-Erhebungsmodule, gelang es ein kurzes Messinstrument mit zuverlässiger und reichhaltiger Datenerhebung zu konzipieren, das folglich in Studien mit großer Proband:innenzahl oder bei Studien mit bereits komplexer bzw. vielfältiger Datenerhebung gut eingesetzt werden kann (Ghotbi et al., 2020).

In einem zweiten Projekt wurden nun Kenntnisse über Chronotypen und sozialen Jetlag in Beziehung zu Nikotinkonsum gestellt und untersucht, da eine signifikant höhere Prävalenz von Nikotinkonsum bei späteren Chronotypen bereits gefunden worden war (Wittmann et al., 2006). Das Projekt ging der Frage der Ursache für diese Assoziation nach: besteht diese da Rauchen die circadiane Uhr später macht oder führt der soziale Jetlag, der bei späteren Chronotypen stark prävalent ist, zum Rauchen als Bewältigungsstrategie? Die Forschungsarbeit kam zu dem Ergebnis, dass Rauchen wahrscheinlicher als Strategie im Umgang mit den negativen Effekten des sozialen Jetlags eingesetzt wird, als dass Rauchen den Chronotyp später macht (Ghotbi et al., 2023).

2.6.1 µMCTQ Validierung: Beitrag zur Beantwortung der übergeordneten Fragestellung

Die Kenntnis über Chronotyp und sozialen Jetlag ermöglicht es das biologische Programm der circadianen Uhr und dessen Interaktionen mit der Umwelt überhaupt untersuchen zu können, da die Chronotypisierung eine wichtige Grundlage chronobiologischer Forschungsvorhaben darstellt (Klerman et al., 2022). So können Zusammenhänge zwischen der Synchronisierung der circadianen Uhr, eventuell bestehendem sozialen Jetlag, und gesundheitlichen sowie therapeutischen Aspekten beleuchtet werden. Vereinfacht einsetzbare und nicht-invasive Messinstrumente tragen dazu bei dies in größerem Rahmen und niedrigschwelliger umsetzen zu können, was für die notwendige Gewinnung großer Datensätze vorteilhaft ist (Ghotbi et al., 2020; Klerman et al., 2022).

2.6.2 Nikotinkonsum und circadiane Uhr: Beitrag zur Beantwortung der übergeordneten Fragestellung

Rauchen wird vielfach als Bewältigungsstrategie im Umgang mit zum Beispiel emotionalen Belastungen, Stress, eingeschränkter Konzentration und Wachheit eingesetzt (Ernst et al., 2001; Fidler and West, 2009; Heishman et al., 2010; Kassel et al., 2003; Lujic et al., 2005; West et al., 2005). Es konnte gezeigt werden, dass diese genannten Belastungsfaktoren bei vorliegendem sozialem Jetlag ausgeprägter sind (Beauvalet et al., 2017; Levandovski et al., 2011; Tamura et al., 2022; Tarokh et al., 2019). Diese Forschungsarbeit trägt somit zur weiteren Kenntnis über die Interaktion der circadianen Uhr des Menschen mit der Umwelt bei und beleuchtet potenzielle Effekte bei Diskrepanzen zwischen Innen- und Außenzeit. Sie verdeutlicht die Rolle der circadianen Uhr und des sozialen Jetlags bei der Entwicklung von Tabaksucht und unterstreicht die Relevanz der Berücksichtigung chronobiologischer Aspekte bzw. sozialen Jetlags bei der Umsetzung von Rauchentwöhnung und Tabakprävention, was angesichts der Gesundheitsrisiken durch Rauchen insbesondere relevant ist (Ghotbi et al., 2023).

3. Zusammenfassung:

3.1 Zusammenfassung µMCTQ Validierung

Der µMCTQ Fragebogen wurde in diesem Projekt aus den zentralen Chronotyp-Modulen des MCTQ generiert. Der µMCTQ ist somit ein neuer Kurz-Fragebogen zur Ermittlung des Chronotyps, des sozialen Jetlags und der Schlafzeiten. In diesem Projekt wurden µMCTQ-Daten mit Daten aus anderen etablierten chronobiologischen Messmethoden verglichen. So erfolgte die Bestimmung des Melatonin-Ausschüttungsprofils im Speichel (DLMO), die als Goldstandard-Methode Auskunft über die Synchronisierungsphase gibt. Ebenfalls wurden aus Aktivitätsdaten und dem MCTQ chronobiologische Schlüsselvariablen (z.B. Chronotyp, sozialer Jetlag) berechnet und mit dem µMCTQ verglichen. Zur vergleichenden Datenanalyse wurden deskriptive Informationen ausgewertet, Korrespondenz-Analysen (Bland-Altman-Analysen), Korrelationsanalysen und Reliabilitätsanalysen durchgeführt. Der µMCTQ erwies sich in der Zusammenschau der generierten Ergebnisse als ein valides und reliables Messinstrument zur Erfassung des Chronotypen und des sozialen Jetlags, durch die Erhebung von Schlafzeiten. Hierbei ist hervorzuheben, dass er durch seine Kürze eine schnelle, effektive, kostensparende und vereinfacht einsetzbare Messmethode darstellt. Dies kann insbesondere für große Kohorten oder Erhebungen mit vielfältigen/komplexen Datenmessungen von Vorteil sein (Ghotbi et al., 2020).

3.2 Zusammenfassung Nikotinkonsum und circadiane Uhr

In dieser Forschungsarbeit wurde die bereits beschriebene Assoziation zwischen sozialem Jetlag, spätem Chronotypen und Nikotinkonsum näher untersucht. Es wurde der Fragestellung nachgegangen ob Rauchen die circadiane Uhr später macht und so zu mehr sozialem Jetlag führt (Hypothese 1) oder ob Rauchen als Strategie im Umgang mit negativen Effekten von sozialem Jetlag, der oft mit spätem Chronotyp einhergeht, eingesetzt wird (Hypothese 2). Zur Beantwortung dieser Frage wurden Raucher:innen bei dem Vorhaben begleitet mit dem Rauchen aufzuhören. Mehrwöchige verhaltenstherapeutische Rauchentwöhnungskurse wurde umgesetzt und fortlaufend Daten der Proband:innen erhoben. Messungen vor und nach Rauchstopp wurden miteinander verglichen und es wurde untersucht ob sich der Chronotyp oder der soziale Jetlag signifikant verändern. Hypothese 1 sollte wahrscheinlicher zutreffen, sollten

tatsächliche Veränderungen durch Rauchstopp festzustellen sein und Hypothese 2 sollte hingegen wahrscheinlicher zutreffen, sollten keine signifikanten Veränderungen zwischen vor und nach Rauchstopp zu ermitteln sein. Es wurden deskriptiv-demographische Daten, kontinuierliche Aktivitätsdaten, Melatonin-Messungen im Speichel, Fragebögen zu chronobiologischen Daten, Schlafqualität und Tagesmüdigkeit erhoben. Ebenso wurden Kohlenmonoxid-Messungen in Atem- und Umgebungsluft durchgeführt. Zur Auswertung wurden Schlüsselvariablen errechnet und binäre logistische Regressionen, Schätzgleichungen, nicht-parametrische Tests und Korrelationsanalysen berechnet Unter Auswertung der genannten Daten ließ sich feststellen, dass keine signifikanten Veränderungen zwischen vor und nach Rauchstopp vorlagen. Dies galt sowohl für die Gruppe der erfolgreich abstinenten Proband:innen, sowie für die weiterhin rauchenden Proband:innen. Ebenso bestanden keine signifikanten Unterschiede vor Interventionsbeginn, die retrospektiv Unterschiede hätten erklären können. In der Zusammenschau der Analyseergebnisse, erscheint Hypothese 2, also dass Rauchen im Umgang mit negativen Auswirkungen von sozialem Jetlag eingesetzt wird, wahrscheinlicher. Die Schlafqualität und Tagesmüdigkeit der Proband:innen lag im auffälligen Bereich und verbesserte sich nicht durch Rauchstopp oder Rauchreduktion. Eine höhere Tagesmüdigkeit war mit scheiternder Rauchentwöhnung assoziiert. Um zu einem fundierten Verständnis der Interaktion von Rauchen und Schlaf/Tagesmüdigkeit zu gelangen, sind weitere Untersuchungen notwendig.

4. Abstract (English):

This dissertation consists of two projects. In the first project a new questionnaire for chronotype-assessment was probed. In the second project the known associations between social jetlag and smoking were investigated regarding its causal mechanisms.

The circadian system of humans, as well as most other organisms, synchronizes individually with the light-dark structure of the environment – resulting in an individual "phase of entrainment" (Duffy and Wright, 2005; Roenneberg et al., 2003a). Being able to assess this individual phase of entrainment is relevant to gathering important chronobiological data, conduct epidemiological studies or to ensure the application of chronotype and other circadian measures in circadian medicine (Klerman et al., 2022). Other established measurements, such as dim-light melatonin onset (DLMO), while still the gold-standard, are arduous and costly, as they rely on multiple measurements in specific conditions (Arendt, 2006; Klerman et al., 2022). Therefore, questionnaires pose an effective and easy-to-use solution for chronotype approximation. To this end, the already established and widely used Munich ChronoType Questionnaire (MCTQ) was reduced to its core chronotype module, consisting of six questions. This questionnaire is thus called the micro Munich ChronoType Questionnaire (µMCTQ). In this study we showed that results from the µMCTQ correspond well to the MCTQ results, as well as to DLMO and actimetry data. Chronotype assessed via the µMCTQ showed a good test-retest reliability and correlation with DLMO and actimetry data. Therefore, the µMCTQ is a suitable instrument to assess chronotype, social jetlag and sleep times in a time-efficient manner, which is especially useful for large study cohorts (Ghotbi et al., 2020).

A strong association between late chronotype, social jetlag and smoking has been described (Wittmann et al., 2006). There are two possible explanations for this association. Either smoking leads to a delay of the circadian clock or smoking is used to cope with negative effects of social jetlag. To investigate the causality further, we followed participants in a smoking cessation program (who did not use nicotine replacement products) and compared their data between before and after cessation. We investigated their sleep-wake behavior as well as sleep quality and daytime sleepiness (via actimetry and questionnaires). Since no effects of cessation were found on circadian parameters (social jetlag, chronotype) or sleep measurements, the second explanatory

scenario seems more likely. Smoking may indeed rather be a consequence of social jetlag than a cause for it. Daytime sleepiness significantly predicted successful or unsuccessful cessation but did not improve upon quitting smoking. Further investigations are needed to better understand the apparent complex relationship between daytime sleepiness/sleep quality and smoking (Ghotbi et al., 2023).

5. Paper I

The μMCTQ: An Ultra-Short Version of the Munich ChronoType Questionnaire

Neda Ghotbi,[*,†,1] Luísa K. Pilz,[*,‡,§,1] Eva C. Winnebeck,[*] Céline Vetter,[||] Giulia Zerbini,[*] David Lenssen,[*] Giovanni Frighetto,[¶] Marco Salamanca,[¶] Rodolfo Costa,[#] Sara Montagnese,[¶] and Till Roenneberg[*,2]

[*]*Institute of Medical Psychology, LMU Munich, Munich, Germany,* [†]*Department of Child and Adolescent Psychiatry, Psychosomatics and Psychotherapy, University Hospital Munich, Munich, Germany,* [‡]*Programa de Pós-Graduação em Psiquiatria e Ciências do Comportamento. UFRGS, Porto Alegre, Brazil,* [§]*Laboratório de Cronobiologia e Sono HCPA/UFRGS, Porto Alegre, Brazil,* [||]*Department of Integrative Physiology, University of Colorado at Boulder, Boulder, Colorado, USA,* [¶]*Department of Medicine, University of Padova, Padova, Italy and* [#]*Department of Biology, University of Padova, Padova, Italy.*

Abstract Individuals vary in how their circadian system synchronizes with the cyclic environment (zeitgeber). Assessing these differences in "phase of entrainment"—often referred to as chronotype—is an important procedure in laboratory experiments and epidemiological studies but is also increasingly applied in circadian medicine, both in diagnosis and therapy. While biochemical measurements (e.g., dim-light melatonin onset [DLMO]) of internal time are still the gold standard, they are laborious, expensive, and mostly rely on special conditions (e.g., dim light). Chronotype estimation in the form of questionnaires is useful in approximating the timing of an individual's circadian clock. They are simple, inexpensive, and location independent (e.g., administrable on- and offline) and can therefore be easily administered to many individuals. The Munich ChronoType Questionnaire (MCTQ) is an established instrument to assess chronotype by asking subjects about their sleep-wake-behavior. Here we present a shortened version of the MCTQ, the μMCTQ, for use in situations in which instrument length is critical, such as in large cohort studies. The μMCTQ contains only the core chronotype module of the standard MCTQ (stdMCTQ), which was shortened and adapted from 17 to 6 essential questions, allowing for a quick assessment of chronotype and other related parameters such as social jetlag and sleep duration. μMCTQ results correspond well to the ones collected by the stdMCTQ and are externally validated by actimetry and DLMO, assessed at home (no measure of compliance). Sleep onset, midpoint of sleep, and the μMCTQ-derived marker of chronotype showed slight deviations toward earlier times in the μMCTQ when compared with the stdMCTQ (<35 min). The μMCTQ assessment of chronotype showed good test-retest reliability and correlated significantly with phase markers from actimetry and melatonin (DLMO), especially with measurements taken on work-free days. Because of its brevity, the μMCTQ represents an ideal tool to estimate individual internal time in time-critical contexts, from large cohort studies to individualized medicine.

Keywords validation, chronotype, phase of entrainment, DLMO, actigraphy, circadian

1. These authors contributed equally to this work.

2. To whom all correspondence should be addressed: Till Roenneberg, Institute of Medical Psychology, LMU Munich, Goethestrasse 31, München, D-80336, Germany; e-mail: roenneberg@lmu.de.

JOURNAL OF BIOLOGICAL RHYTHMS, Vol. XX No. X, Month 201X 1–13
DOI: 10.1177/0748730419886986

Our daily lives are controlled by at least 2 "clocks," which historically used to be in phase: (1) the sun clock that defines day and night, dawn and dusk, or photoperiod that—depending on latitude—changes over the year and (2) social clocks that represent "local time" and allow us to interact with others (school, work, business hours). Over the course of history, we introduced time zones and Daylight Saving Time (DST), thereby separating local time and sun time. Circadian clocks synchronize to the 24-h day predominately through light and darkness, but the strength of this zeitgeber has greatly decreased during industrialization, as humans live predominantly in buildings throughout the day and artificially illuminate the nights. Everyone's circadian system establishes its own specific phase relationship with the zeitgeber cycle (phase of entrainment [PoE]), evidenced by the difference in timing of biological rhythms in reference to the light-dark cycle between individuals, for example, melatonin, temperature, peak of activity/activity onset, peak of cortisol, or behavioral timing like that of sleep and wake (Roenneberg et al., 2003a). These differences in PoE are commonly called chronotype, ranging from extreme early chronotypes (larks) to extreme late chronotypes (owls). As a consequence of the changed light-dark cycles, the PoE of extreme early types has become even earlier and that of all the other chronotypes has become delayed, greatly widening the difference between early and late chronotypes, especially within urban populations (Roenneberg et al., 2007b; Stothard et al., 2017; Swaminathan et al., 2017; Wright et al., 2013).

Since practically all functions in our body are directly or indirectly organized by the circadian clock, temporal inconsistencies between biological and social timing become problematic, increasing the need to estimate individual internal time (PoE, chronotype, circadian phase) in research or medicine (from diagnosis to treatment). The gold standard for assessing circadian phase is measuring dim-light melatonin onset (DLMO) in samples collected in highly controlled settings, in blood, urine, or saliva (Benloucif et al., 2008; Klerman et al., 2002; Lewy and Sack, 1989). However, these measurements are expensive and cumbersome, involving multiple, well-timed samplings. Although circadian researchers are currently developing methods to assess circadian state with 1 to 2 measurements, these so far still require sampling blood, involving many known complications that limit their application in large-scale studies (Braun et al., 2018; Laing et al., 2017; Wittenbrink et al., 2018). A cost-effective, scalable, and noninvasive solution to this challenge is the use of questionnaires.

The first questionnaire developed to detect individual differences in circadian rhythms, the Morningness-Eveningness Questionnaire, uses temporal preferences to compute a score and classify individuals into chronotypes accordingly (Horne and Ostberg, 1976). The Munich ChronoType Questionnaire (MCTQ), on the other hand, was introduced in 2003 (Roenneberg et al., 2003b) and considers chronotype as the phase relationship between the circadian system of an individual and the zeitgeber cycle: their circadian state. Since it is virtually impossible to assess the phase of all rhythmic processes in humans, the MCTQ uses sleep timing as a phase marker to estimate chronotype. The standard core questions inquire about sleep times separately for work and work-free days. Considering that sleep on work-free days is not as restricted by social constraints, chronotype can be estimated using the midpoint between sleep onset and sleep end on free days (MSF), which is corrected for potential oversleep on free days (to compensate for sleep debt accumulated over the workweek, MSF_{sc}), therefore accounting for the homeostatic process influencing sleep. Other modules assess the use of stimulants or biographic information, for example.

The stdMCTQ-MSF_{sc} has already been shown to correlate well with data from sleep logs, wrist actimetry, and DLMO (Kantermann et al., 2015; Kitamura et al., 2014; Roenneberg et al., 2007a; Wright et al., 2013). It has been used for 15 years to assess thousands of peoples' sleep behavior (the MCTQ database associated with its online version alone contains ≈300,000 entries).

Thus, the µMCTQ was developed as an ultra-short version of the stdMCTQ. This questionnaire makes use of the same principles as the stdMCTQ but contains only the essential questions of the MCTQ's core chronotype module. As with the stdMCTQ, MSF_{sc} serves as a marker for chronotype and an approximation for PoE. The µMCTQ therefore allows for a swift assessment of the timing of an individuals' clock, which can be especially useful in larger cohort studies, long durations of investigation, or for efforts of personalized medical practice.

Here we present the validation of the circadian phase assessment by the µMCTQ against assessments by the stdMCTQ (study 1) as well as DLMO and actimetry (study 2). In the supplementary material, we provide additional data supporting the validity of the stdMCTQ for assessing PoE (study 3). Our results show that both the µMCTQ and the stdMCTQ have good validity against commonly used physiological and behavioral markers of PoE.

METHODS

Development of the µMCTQ

The µMCTQ was developed starting from the original MCTQ (Roenneberg et al., 2003b), in the following referred to as standard MCTQ (stdMCTQ).

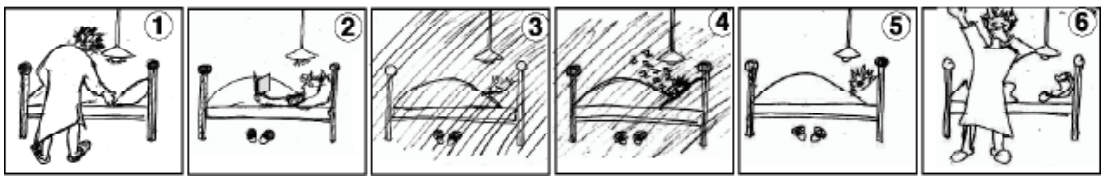
Munich ChronoType Questionnaire (MCTQ)

I have a regular work schedule (this includes being, for example, a housewife or househusband):

Yes ☐ I work on 1☐ 2☐ 3☐ 4☐ 5☐ 6☐ 7☐ days per week.

No ☐

Is your answer "*Yes, on 7 days*" or "*No*", please consider if your sleep times may nonetheless differ between regular 'workdays' and 'weekend days' and fill out the MCTQ in this respect.



Please use 24-hour time scale (e.g. 23:00 instead of 11:00 pm)!

Workdays

Image 1: I go to bed at _____ o'clock.

Image 2: Note that some people stay awake for some time when in bed!

Image 3: I actually get ready to fall asleep at _____ o'clock.

Image 4: I need _____ minutes to fall asleep.

Image 5: I wake up at _____ o'clock.

Image 6: After _____ minutes I get up.

I use an alarm clock on workdays: Yes ☐ No ☐

If "Yes": I regularly wake up BEFORE the alarm rings: Yes ☐ No ☐

Free Days

Image 1: I go to bed at _____ o'clock.

Image 2: Note that some people stay awake for some time when in bed!

Image 3: I actually get ready to fall asleep at _____ o'clock.

Image 4: I need _____ minutes to fall asleep.

Image 5: I wake up at _____ o'clock.

Image 6: After _____ minutes I get up.

My wake-up time (Image 5) is due to the use of an alarm clock: Yes ☐ No ☐

There are particular reasons why I cannot freely choose my sleep times on free days:

Yes ☐ If "Yes": Child(ren)/pet(s) ☐ Hobbies ☐ Others ☐, for example:_____

No ☐

Figure 1. The core module of the standard Munich ChronoType Questionnaire (stdMCTQ) asks questions about sleep timing in relation to the weekly structure. It does so by leading the sleeper in and out of bed in 6 steps, both for workdays and work-free days. In total, participants need to answer 14 to 17 questions (depending on specific answers). On a separate page, participants are given instructions on how to fill in the stdMCTQ, for example, "take an example month" or "according to the past 4 weeks."

The stdMCTQ asks simple questions about sleep-wake behavior, separately for work and work-free days. Its core module, which focuses on the estimation of chronotype, contains a total of 17 questions (other optional modules, e.g., regarding the use of stimulants and sociodemographics have varying lengths). The original idea of the stdMCTQ core questions was to accompany people into and out of bed (see Fig. 1 for the complete questionnaire). Since sleep onset (falling asleep) and bed time (going to

µMCTQ

The following section will ask you questions in regards to your sleep and wake behavior on work- and work-free days. Please estimate an average of your 'normal' sleep behavior over the past 6 weeks.

I have been a shift- or night-worker in the past three months yes __ no __

Normally, I work _____ days/week.

Please answer all the following questions even if you do not work or work 7 days/week. Please don't forget to circle AM or PM.

On WORKDAYS …
… I normally fall asleep at __:__ AM/PM (this is NOT when you get into bed, but rather when you fall asleep)

… I normally wake up at __:__ AM/PM (this is NOT when you get out of bed, but rather when you wake up)

On WORK-FREE DAYS when I DON'T use an alarm clock …
… I normally fall asleep at __:__ AM/PM (this is NOT when you get into bed, but rather when you fall asleep)

… I normally wake up at __:__ AM/PM (this is NOT when you get out of bed, but rather when you wake up)

Figure 2. The entire ultra-short version of the Munich ChronoType Questionnaire (µMCTQ) consists of a short explanatory introduction, 2 work-related questions, another short instruction, and 2 questions about sleep timing each for work and work-free days. Thus, participants have to answer 6 questions in total.

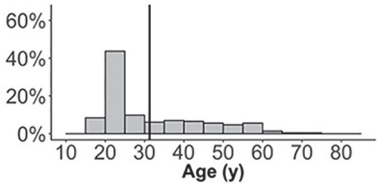
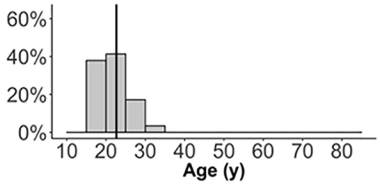
bed) are often confused, we asked people questions about every step: (1) going to bed, (2) being busy in bed before deciding (3) to prepare for sleep (e.g., by switching off lights), (4) falling asleep (the last 2 indicate sleep latency), (5) waking up, and (6) finally getting up (the last 2 indicate sleep inertia). The stdMCTQ and more information on it can be found at http://thewep.org/documentations/mctq.

Naturally, in aiming for brevity, the µMCTQ (Fig.2) contains only questions from the core chronotype module of the stdMCTQ and no questions from the optional additional stdMCTQ modules. The core module was then reduced to questions pertaining to the core variables, which were slightly modified but are content-wise identical. Since only sleep onset and sleep end as well as the weekly structure are used to calculate the most important stdMCTQ variables (MSF, MSF_{sc}, sleep duration, and social jetlag), we reduced the 17 questions to 6 questions, probing only these events. We also tried to make participants aware that we do not mean bedtime or rise time but actual time of falling asleep or waking up.

Both the stdMCTQ and the µMCTQ estimate chronotype in 2 steps. First, the midpoint of sleep on work-free days (MSF) is calculated based on sleep onset (SO_f) and sleep end (SE_f): $MSF = SO_f + (SE_f - SO_f)/2$, whereby ($SE_f - SO_f$) provides the sleep duration on work-free days (SD_f). The same variables can be assessed for workdays: midpoint of sleep on workdays ($MSW = SO_w + (SE_w - SO_w)/2$) and sleep duration on workdays ($SD_{w =} SE_w - SO_w$).

The second step to compute the chronotype indicator is to further correct MSF for the potential sleep debt accumulated during the workweek. This linear correction is based on the weighted average of sleep duration across the week (SD_{week}) and on the sleep duration on work-free days (SD_f). The difference of the two is taken as an estimate for how much longer subjects slept on a work-free day (versus if they had no prior sleep debt, when $SD_f \leq SD_w$): if $SD_f \leq SD_w$, $MSF_{sc} = MSF$; if $SD_f > SD_w$, $MSF_{sc} = MSF - (SD_f - SD_{week})/2$. Free days are used for chronotyping, as those are the days assumed to be relatively free of constraints on sleep-wake behavior. In the stdMCTQ, participants are asked to specify the need of an alarm clock ("yes" or "no" answer): MSF_{sc} calculations are considered only when the participant does not use/need an alarm clock on work-free days. In the µMCTQ, however, participants are asked to report their wake-up times only on work-free days on which they do not use an alarm clock. Therefore MSF_{sc}, derived from the µMCTQ can be

Table 1. Data set characteristics.

	µMCTQ vs. stdMCTQ (study 1; ***N*** = 213)	µMCTQ vs. DLMO/Ψ_Act (study 2; ***N*** = 29)
Female sex, ***n*** (%)	129 (61)	13 (45)
Age, y, mean ± SD	31.3 ± 13.0 (range: 18-75)	22.7 ± 3.6 (range: 19-33)
Age distribution of the sample		
Validation study variables		
MSF_{sc}, h, mean ± SD	stdMCTQ: 4:45 ± 1:13 µMCTQ: 4:29 ± 1:14	4:27 ± 1:01
DLMO, h, mean ± SD		WD: 21:25 ± 1:16 FD: 22:05 ± 1:28
Ψ_Act, h, mean ± SD		16:12 ± 1:05 WD: 15:54 ± 0:59 FD: 16:47 ± 1:24

Data sets used in the study for validating the µMCTQ against the stdMCTQ (column 1) and for validating the µMCTQ against DLMO and Ψ_Act (column 2). stdMCTQ = standard Munich ChronoType Questionnaire; µMCTQ = ultra-short version of the stdMCTQ; MSF_{sc} = midpoint between sleep onset and end on free days corrected for potential oversleep on free days to compensate for the sleep debt accumulated over the workweek; DLMO = dim-light melatonin onset; Ψ_Act: center of gravity of activity; WD = workday; FD = free day.

computed for all subjects. A detailed overview of the calculations of the mentioned variables can also be found in the supplementary material (Suppl. Table S2).

Validation of the µMCTQ

The validation of the µMCTQ against the stdMCTQ was carried out at the University of Padova, Italy, and is further referred to as study 1. The study for the validation of the µMCTQ against the phase markers from melatonin (DLMO) and actimetry data was carried out at the Ludwig Maximilian University in Munich, Germany, and is referred to as study 2. Data supporting the validity of the stdMCTQ against actimetry are included in the supplementary material and referred to as study 3.

The Italian version of the µMCTQ, used in study 1, was obtained by the Sackett procedure (i.e., forward translation, expert evaluation, independent back-translation, pretesting, and definition of the final version). The German µMCTQ version used in study 2 was a simple translation from the English µMCTQ version into German. Both translated versions (German and Italian) ask individuals to use the 24-h military time format (e.g., 23:00 h instead of 11:00 p.m.). Table 1 offers an overview of the different sample characteristics in the different studies. Detailed descriptions of the study designs can be found below.

Study 1: Validation of the µMCTQ against the stdMCTQ

Participants. For the validation of the µMCTQ against the stdMCTQ, we recruited 361 healthy volunteers as part of a series of popular science initiatives (open Padova University event "Veneto Research Night" 2015) during which Padova University scientists provided the general public with information on their ongoing research. Forty-eight subjects were excluded because of significant medical history, shift work, and/or incomplete questionnaire responses. Because of alarm clock use on free days, 87 participants were excluded from all analyses. Thus, the final population included 213 individuals (129 women; age [mean ± standard deviation]: 31.3 ± 13.0 years). See Table 1 for further details.

Study Design. Subjects completed a personal datasheet to include basic demographic and medical information, height, and weight before they filled out the Italian translations of the µMCTQ followed by the stdMCTQ (always in the same sequence). The researchers G.F., M.S., and S.M. provided assistance and instructions on completion of the questionnaires. Participants provided written, informed consent.

Measurements. Participants filled in the µMCTQ (time span referring to the past 6 weeks) and stdMCTQ (referring to a "regular week").

Statistical Analyses

Bland-Altman plots. The relationship between the µMCTQ and the stdMCTQ was studied using Bland-Altman plots (Bland and Altman, 1986, 1999). The Bland-Altman plot is a graphical method to compare 2 measurements techniques: the differences between the measurements obtained by the 2 techniques are plotted against the average of the measurements. Horizontal lines are drawn at the mean difference and at the 95% limits of agreement, which are defined as the mean difference ±1.96 times the standard deviation of the differences. If these limits do not exceed the maximum "allowable" difference between the methods (i.e., the differences are not yet physiologically or clinically relevant), the 2 measurement methods are considered to be in agreement and can be used interchangeably. Finally, if some degree of correlation exists between the differences and the averages on the Bland-Altman plot, the over- or underestimation of one method versus the other increases/decreases depending on the absolute value or size of the measurement. Since the differences between measurements were not normally distributed, correlations were tested using Spearman's rho.

Correlations. Correlations between variables from the stdMCTQ and the µMCTQ were tested using Pearson's *r*, since all variables were nearly normally distributed (inspection of histograms).

Study 2: Validation of the µMCTQ against Activity and Melatonin Phase (DLMO)

Participants. Thirty participants (15 women, age [mean ± standard deviation]: 22.7 ± 3.6 years) were recruited by convenience sampling (mostly students recruited by flyers on campus). Exclusion criteria were irregular work schedules or shift work or a transmeridian flight during a 3-month period prior to study participation. All participants provided informed consent; the study was approved by the Ethics Committee of Ludwig Maximilian University (approval 517-15) and conducted in accordance with the Declaration of Helsinki.

Study Design. Because of reasons of feasibility, the study spanned the autumn DST change. The cohort was divided into 2 groups. Group 1 (G1; 9 women and 6 men) started the study shortly before the DST change in October 2015 and was monitored for 6 weeks. Group 2 (G2; 6 women and 9 men) started a week after the time change and was monitored for 4 weeks. One subject (from G1) did not fill in the questionnaire correctly and had to be excluded.

Participants filled out the µMCTQ once at study onset. Throughout the course of the study, they filled out an online version of the µMCTQ on a daily basis (similar to a sleep-log), but the daily assessments were used only to generate date-type data (work- or work-free day).

Measurements. In addition to the µMCTQ, actimetry and home DLMO data were collected for circadian phase determination. In G1, saliva samples were collected during the first week before the time change, and the µMCTQ was filled in 8 days before the time change. In G2, saliva samples were taken in the second week after the time change, and the µMCTQ was answered 5 days after the time change.

Activity phase assessment. Actimeters are wrist-worn devices that measure locomotor activity by accelerometry. Devices (Daqtometers by Daqtix GmbH) were worn throughout the entire study period (G1: 6 weeks, G2: 4 weeks). Recordings from G1 before the DST change and the first week after the time change were excluded from the analyses. Activity was recorded at 1 Hz, and the average activity counts were stored every 30 s. For analyses, data were averaged into 10-min bins. Participants kept a diary about day types (work or work-free days). We used the software ChronoSapiens (Chronsulting UG; Roenneberg et al., 2015) to assess the daily phase of general locomotor activity measured by the wrist-worn actimeters. For every day, we calculated the acrophase of the best 1-harmonic, 24-h cosine fit (Ψ_Act). The advantage of this phase marker is that it does not rely on any other computations of the actimetry signal such as algorithms identifying sleep. Ψ_Act for every subject was calculated using daily averages across all days. Individual averages were also calculated separately for workdays (Ψ_Act_w) and work-free days (Ψ_Act_f). For the calculation of the general Ψ_Act results, we also included days not specified as work or work free. Data are expressed as local time.

DLMO assessment. DLMO was assessed at home in this study for reasons of feasibility. Home DLMOs have previously been reported to show a good correspondence to lab DLMOs (Burgess et al., 2015; Pullman et al., 2012), especially when participants' compliance is being objectively monitored (which, however, was not the case in our study). Participants had an appointment with study team members, during which they were instructed on how to collect saliva samples. The volunteers were asked to collect 7 saliva samples hourly once on a workday and once on a work-free day starting 6 h before their usual sleep timing. Subjects were told to close the blinds and turn off as many lights as possible 1 h before saliva collection started and were given blue light–blocking sunglasses to wear during the period of collection. They

were also instructed to dim screen lights of electronic devices, not to change their position at least 5 min before taking the sample, and to rinse their mouth with clear water before collection. They were also told not to eat chocolate or bananas or to drink coffee or alcohol during the period of saliva collection. A written version of the instructions was provided as well. Samples were collected using Salivette cotton swabs (Sarstedt AG & Co.). The participants wrote down the times of collection into a log provided by the study team, without further measures of compliance, and they kept the samples in the fridge (~4°C) until bringing them to the laboratory (storage duration <7 days), where they were processed and kept at −20°C until further use (storage duration <3 months). The duration of sample storage was in accordance with manufacturer guidelines.

Chrono@work (Groningen, the Netherlands) analyzed the samples. Melatonin concentrations were assessed using direct saliva melatonin radioimmunoassay test kits (RK-DSM; Bühlmann Laboratories, Alere Health, Tilburg, the Netherlands). DLMO was calculated by linear interpolation between the time points before and after melatonin concentrations crossed and stayed above the threshold of 3 pg/mL. We opted for the fixed threshold method for sample size reasons (insufficient points to calculate baseline for some individuals), but similar results were seen using the threshold of 2 standard deviations above the baseline (see Suppl Fig. S8). The lower limit detection of the kit was 0.3 pg/mL. The intra-assay variability was 15.9% at low melatonin concentration (mean = 2.0 pg/mL, n = 17) and 13.1% at high melatonin concentration (mean = 24.5 pg/mL, n = 15). The interassay variability was 13.1% at low melatonin concentration (mean = 2.0 pg/mL, n = 16) and 15.0% at high melatonin concentration (mean = 21.4 pg/mL, n = 16). DLMO on a workday could be calculated from 24 individuals and DLMO on a work-free day from 25 individuals.

Statistical Analyses. Shapiro-Wilk test and inspection of histograms were used to test the variables for normality, and all variables showed a normal distribution. Correlations between MSF_{sc} (as assessed by the µMCTQ) and DLMO as well as the different Ψ_Act values were tested using Pearson's correlation. An alpha level of 0.05 was chosen. SPSS 24 and GraphPad Prism 6 were used for statistical analyses. Graphs were plotted using the R package ggplot2 (Wickham, 2016).

Test-Retest Reliability. We performed test-retest measurements in 37 subjects to test chronotype reliability (µMCTQ-MSF_{sc}) over 2 different time frames. We correlated assessments taken 56 to 63 or 14 to 18 days apart. Twenty students filled in the English version of the µMCTQ (age [mean ± SD]: 23.8 ± 3.3 years; 40% female; interval between assessments: 56-63 days). Eighteen subjects recruited through snowball sampling filled in the German or English online versions of the µMCTQ (age [mean ± SD]: 33.5 ± 7.8 years; 39% female; interval between assessments: 14-18 days).

RESULTS

Study 1: Validation of the µMCTQ against the std-MCTQ

Generally, sleep timing and MSF_{sc} corresponded well between the µMCTQ and stdMCTQ but showed systematic deviations toward earlier times in the µMCTQ in most of the assessed variables.

The µMCTQ estimated sleep onset on workdays and work-free days (SO_w and SO_f) earlier than the stdMCTQ (mean difference ± SD: SO_w 24.7 ± 28.4 min and SO_f 30.8 ± 37.7 min; Fig. 3), with limits of agreement of less than 120 min: −30.9 to 80.3 min for workdays and −42.1 to 104.7 min for work-free days.

In contrast, the 2 tools produced similar estimates for sleep end on both workdays and work-free days (mean difference ± SD: SE_w −2.7 ± 19.0 min, SE_f 2.0 ± 28.7 min; Fig. 4), with a limit of agreement of less than 60 min: SE_w −39.9 to 34.6 min, SE_f −54.3 to 58.3 min.

The average estimate of mid-sleep on workdays (MSW) and on work-free days (MSF) produced by the µMCTQ was less than 20 min earlier than that of the stdMCTQ (MSW mean difference ± SD: 11.0 ± 17.1 min; MSF mean difference ± SD: 16.4 ± 24.7 min; Fig. 5). MSF_{sc} was estimated as less than 20 min earlier by the µMCTQ than by the stdMCTQ (MSF_{sc} mean difference ± SD: 16.3 ± 27.1 min; Fig. 5). Their limits of agreement ranged from about 30 to 70 min: MSW −22.5 to 44.5 min, MSF −32.0 to 64.9 min; MSF_{sc} −36.8 to 69.4 min.

Correlations between the µMCTQ and stdMCTQ in terms of sleep onset (workdays and work-free days), sleep end (workdays and work-free days), MSF, MSW, and MSF_{sc} were all statistically significant and produced coefficients ranging from 0.89 to 0.95 (Suppl. Fig. S1). The same correlations are shown in Supplementary Figures S2 to S4 differentiated into age categories.

Study 2: Validation of the µMCTQ against Activity (Ψ_Act) and Melatonin Phase (DLMO)

MSF_{sc}, as an indicator of chronotype, showed a moderately positive correlation with Ψ_Act and Ψ_

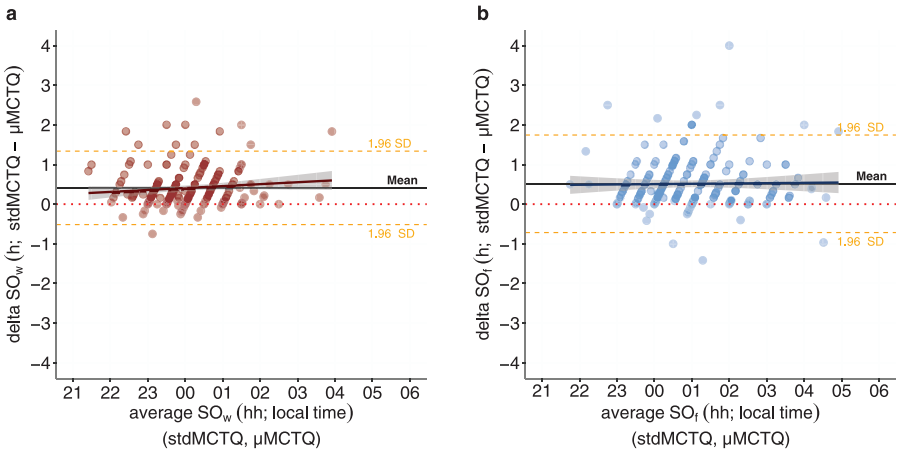


Figure 3. Bland-Altman plots of sleep onset on workdays (a) and work-free days (b) (method- differences on the *y*-axis versus method averages on the *x*-axis). The mean ± 1.96 SD limits of agreement, together with the regression line and pertinent confidence interval, are also depicted in the plot. Of the sample, (a) 6% and (b) 7% were out of the limits of agreement, respectively. Correlation analysis: (a) Spearman's rho 0.11 (ns); (b) 0.01 (ns). SO_w = sleep onset on workdays; SO_f = sleep onset on work-free days. N = 213 (study 1: validation of the ultra-short version of the Munich ChronoType Questionnaire [µMCTQ] against the standard MCTQ [stdMCTQ]).

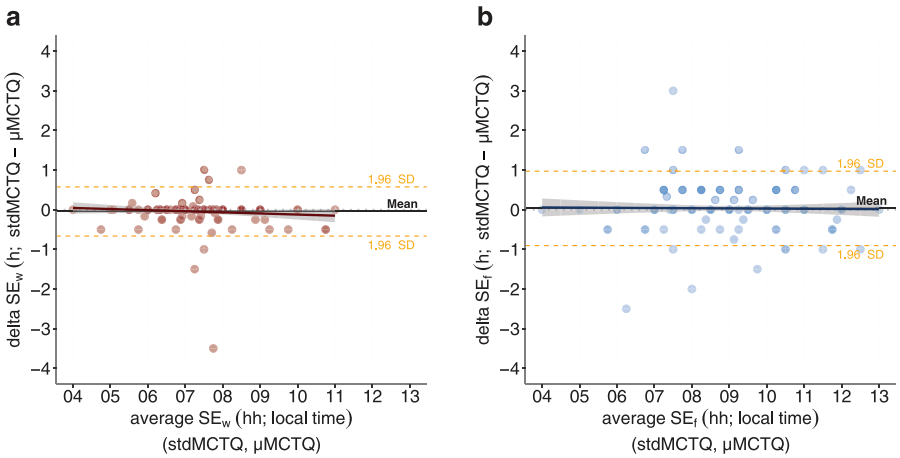


Figure 4. Bland-Altman plots of SE_w (a) and SE_f (b) (method differences on the *y*-axis versus method averages on the *x*-axis). The mean ± 1.96 SD limits of agreement, together with the regression line and pertinent confidence interval, are also depicted in the plot. Of the sample, (a) 3% and (b) 8 were out of the limits of agreement, respectively. Correlation analysis: (a) Spearman's rho −0.10 (ns); (b) −0.04 (ns). SE_w = sleep end on workdays; SE_f = sleep end on work-free days. N = 213 (study 1: validation of the ultra-short version of the Munich ChronoType Questionnaire [µMCTQ] against the standard MCTQ [stdMCTQ]).

Act_f and a tendency to correlate with Ψ_Act_w (Fig. 6). Correlations of MSW and Ψ_Act_w as well as MSF and Ψ_Act_f are provided in the supplementary material (Suppl. Fig. S6).

MSF_{sc} was positively associated with $DLMO_f$ but not with $DLMO_w$ (Fig. 7). Correlations of MSW and $DLMO_w$ as well as of MSF and $DLMO_f$ are provided in the supplementary material (Suppl. Fig. S7).

The µMCTQ showed good test-retest reliability within different time frames (see the Methods section: ~60 days: Pearson's $r = 0.77$, $p < 0.001$; ~14 days: Pearson's $r = 0.79$, $p < 0.001$; Suppl. Fig S9).

DISCUSSION

Our results show that both the µMCTQ and the stdMCTQ are valid instruments to assess PoE and that the 2 questionnaires show good correspondence with each other. The indicator of chronotype (MSF_{sc}), as measured by the µMCTQ, correlates with the timing of both melatonin (DLMO) and activity (Ψ_Act; center of gravity of best fit). We also replicate previous findings, showing the stdMCTQ to correspond with actimetry measures (see the supplementary material).

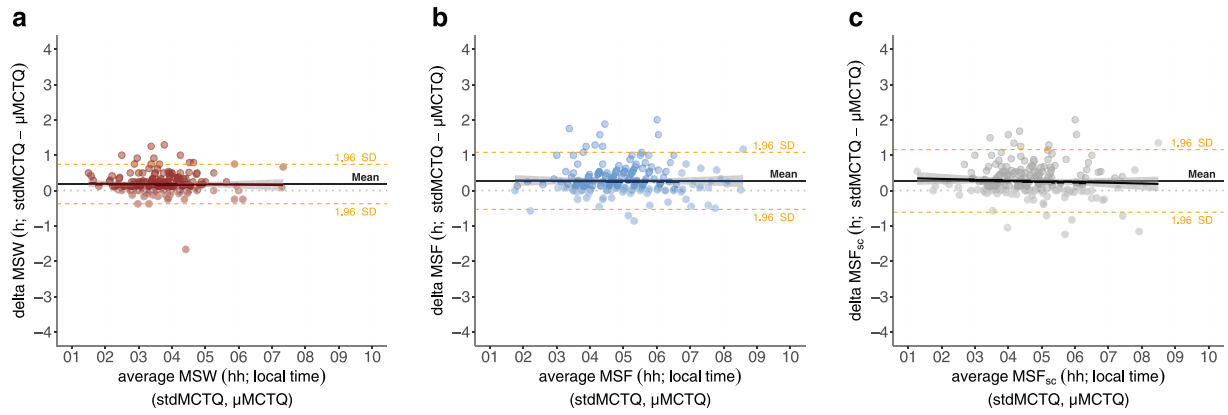


Figure 5. **Bland-Altman plots of (a) MSW, (b) MSF, and (c) MSF$_{sc}$ (method differences on the *y*-axis versus method averages on the *x*-axis). The mean ± 1.96 SD limits of agreement, together with the regression line and pertinent confidence interval, are also depicted in the plot. Of the sample, (a) 7%, (b) 6%, and (c) 7% were out of the limits of agreement, respectively. Correlation analysis: (a) Spearman's rho –0.01 (ns); (b) –0.01 (ns); (c) –0.07 (ns). MSW = midpoint of sleep on workdays; MSF = midpoint of sleep on work-free days; MSF$_{sc}$ = indicator of chronotype, midpoint of sleep on work-free days corrected for sleep debt accumulated over the workweek. *N* = 213 (study 1: validation of the ultra-short version of the Munich ChronoType Questionnaire [µMCTQ] against the standard MCTQ [stdMCTQ]).**

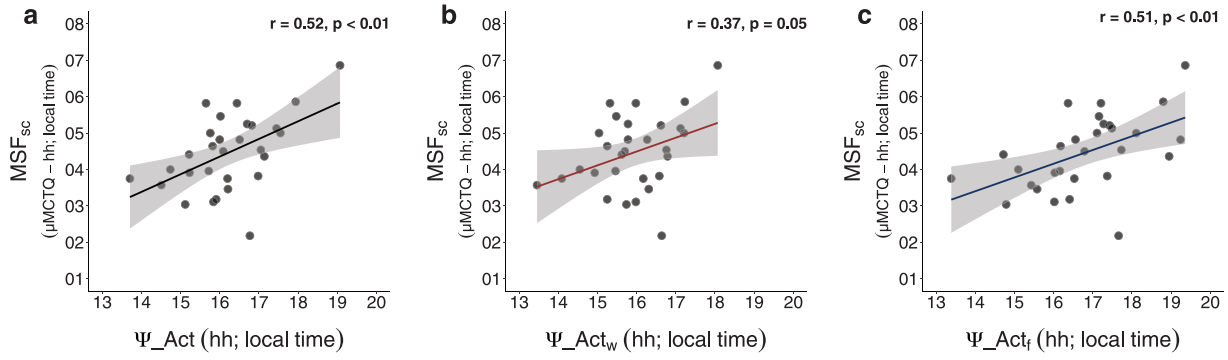


Figure 6. **Associations between MSF$_{sc}$ from the ultra-short version of the Munich ChronoType Questionnaire (µMCTQ) and actimetry phase (Ψ_Act). MSF$_{sc}$ correlates significantly with Ψ_Act (a) as well as with Ψ_Act on work-free days (Ψ_Act$_f$, c), but tended to be associated with Ψ_Act only measured on workdays (Ψ_Act$_w$; b). The gray-shaded area around the regression line represents the 95% confidence interval. Results of Pearson correlations are provided in each graph. Data are expressed in local time for both variables. *N* = 29 (study 2: validation of the µMCTQ against actimetry).**

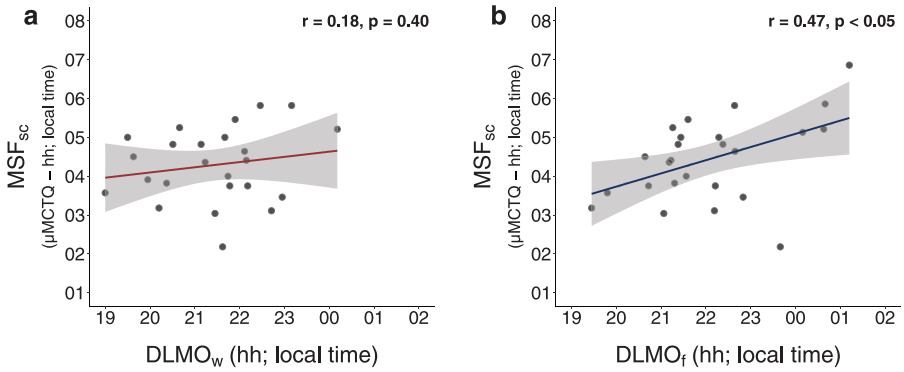


Figure 7. **Association between MSF$_{sc}$ from the ultra-short version of the Munich ChronoType Questionnaire (µMCTQ) and dim-light melatonin onset (DLMO). MSF$_{sc}$ correlates significantly with DLMO measured on work-free days (DLMO$_f$, b) but not with DLMO measured on workdays (DLMO$_w$, a). The gray-shaded area around the regression line represents the 95% confidence interval. Results of Pearson correlations are provided in each graph. Data are expressed in local time for both variables. *n* = 24 to 25 (study 2: validation of the µMCTQ against DLMO). DLMO was collected at home with no objective measures of compliance.**

Correspondence between µMCTQ and stdMCTQ

Overall, all measurements derived from the µMCTQ and the stdMCTQ are in good agreement with each other. The µMCTQ yielded slightly earlier results for sleep onset and thus also for MSW, MSF, and MSF_{sc}. A likely reason for this systematic difference in onset timing is that the µMCTQ lists and asks about less detail on the "going-to-bed-and-falling-asleep process." The µMCTQ does not lead people in and out of bed but asks directly for the time that participants usually fall asleep. Some participants may interpret this as the time when they were prepared to sleep and would therefore indicate an earlier time than actual sleep onset depending on their sleep latency. Alternatively, some people may misinterpret the detailed descriptions in the stdMCTQ explaining the different stages from going to bed to getting up (Fig. 1). For example, different people may have different concepts of what "sleep preparation" means. Does sleep preparation include sleep latency or not? Since the stdMCTQ calculates sleep onset by adding sleep latency to the time people indicate for preparing for sleep, latency might occasionally be added twice. The average sleep latency in the MCTQ database is 15.4 ± 15.2 min for free days and 18.8 ± 17.5 minutes for workdays. Notably, sleep end was not different between µMCTQ and stdMCTQ. An earlier estimate of sleep onset also influences MSW, MSF, and MSF_{sc}. A difference of less than 20 min for MSF_{sc} is lower than the median intraindividual variance of Ψ_Act_f observed in our study (MCTQ study median: 110 min, Q1-Q3: 40-250 min; µMCTQ study median: 126 min, Q1-Q3: 76-192 min) and is well within the variance of both questionnaires and other instruments.

Furthermore, correlations of the stdMCTQ with Ψ_Act (Suppl. Fig. S10) were not significantly stronger than those of the µMCTQ with the same measurement (Ψ_Act_f vs. stdMCTQ-MSF_{sc} and Ψ_Act_f vs. µMCTQ-MSF_{sc}: Fisher's Z test, $z = 0.26$, ns; Ψ_Act vs. stdMCTQ-MSF_{sc} and Ψ_Act vs. µMCTQ-MSF_{sc}: Fisher's Z test, $z = -0.06$, ns).

Both the µMCTQ and the stdMCTQ chronotype showed good test-retest reliability (see Suppl. Figs. S9 and S12). Regarding the stability of our chronotype estimation, we expect the indicator variable to vary across time. This is because we are estimating chronotype as circadian state. Transient state constructs, in contrast to more enduring trait dispositions, are expected to be susceptible to influences from the environment (Boyle et al., 2015). Yet, circadian phase (estimated both using MSF and DLMO) has been shown to be fairly reproducible over months (Kantermann and Eastman, 2018).

Validation of the µMCTQ against Actigraphy and DLMO

µMCTQ-MSF_{sc} correlated with DLMO and Ψ_Act on work-free days but was not significantly correlated with either of these markers on workdays. Since it is assumed that MSF_{sc} reflects an estimation of PoE less affected by social constraints, a weaker correlation with parameters gathered on workdays ($DLMO_w$, Ψ_Act_w) was expected. DST, which occurred during the participation of half the subjects, might have also contributed to the observed result. The µMCTQ assesses sleep behavior in the past 6 weeks, and the second group filled out the questionnaire and measured DLMO 1 week after the time change. The release from DST causes a delay in Ψ_Act and in sleep timing that is more gradual on workdays than on work-free days. It was also shown that the process of adjustment to the time change and how long this process takes is chronotype specific, with late types delaying more readily (Kantermann et al., 2007). The transition accentuates the misalignment between internal time and sleep on workdays, which may be reflected in our data.

Although DST might have influenced our results, µMCTQ-MSF_{sc} was still significantly correlated with DLMOf, similarly to what has been shown in other publications using the stdMCTQ. Even stronger correlations between MSF_{sc} (as per the stdMCTQ) and DLMO (home or lab) have been previously reported (Facer-Childs et al., 2019; Kantermann et al., 2015; Wright et al., 2013). However, when comparing the strength of correlations found in our study (µMCTQ validation) to the ones cited, a significant difference is detectable only between our data and data from Facer-Childs et al. (Fisher's $z = -2.1$, $p < 0.05$). Their data, however, show a wider range in DLMO and MSF_{sc}, as Facer-Childs et al. selected for extreme chronotypes. Correlations are known to be sensitive to data distribution (Goodwin and Leech, 2006), and therefore, we propose the observed differences in correlation strength to likely be attributed to this.

Study Limitations

1. The different age ranges in the cohorts should be noted, as study 2 was conducted in young students with a narrow age range. Nevertheless, correspondence between the questionnaires was good across different age categories (as shown in Suppl. Figs. S2 to S4). As the stdMCTQ was shown to be valid against Ψ_Act in a sample with a wide age range (18-81 years old; see supplementary material), and the µMCTQ corresponds well with the stdMCTQ

in all aspects, we do anticipate similar validations at higher ages. Furthermore, the Korean stdMCTQ has already been shown to be valid against actimetry and sleep logs in a large sample of older adults (≥65 years, N =192, Ryu et al., 2018).

2. In study 2, we acquired a small, homogeneous sample consisting of mostly young university students, which could potentially affect generalizability, and a release from DST occurred in half the subjects while recording actimetry data. Still, MSF_{sc} was significantly correlated to both DLMO and Ψ_Act when they were taken on work-free days, despite the small sample size.
3. The µMCTQ was administered at the beginning of the study and refers to the previous 6 weeks, not corresponding with the time monitored by actimetry. The questionnaire was administered at the beginning to avoid a bias in subjects' responses, since daily assessments of sleep timing were also implemented.
4. The µMCTQ in study 2 was administered in a translated German version without back-translation into English (original language).
5. The µMCTQ was reduced from the stdMCTQ in an intuitive manner, rather than using more objective dimension reduction techniques.
6. DLMO assessment in study 2 was done at home with no measures of compliance, and self- reported collection times in DLMOs assessed at home can be rather inaccurate (Kudielka et al., 2003). However, studies have compared lab-based and home-measured DLMOs and found significant correlation between the 2 conditions regardless of measuring compliance (Burgess et al., 2015; Pullman et al., 2012). Furthermore, Pullman et al. (2012) considered the at-home assessments of DLMO to be satisfactorily accurate (compared with the corresponding lab measurements) in 62.5% to 75% of the cases.

Comparison between µMCTQ and stdMCTQ

As a shortened questionnaire, the µMCTQ naturally collects less information about peoples' sleep behavior than the stdMCTQ. The µMCTQ does not enable the estimation of sleep latency or inertia. Furthermore, in contrast to the stdMCTQ, the µMCTQ does not inquire about reasons for externally induced waking on work-free days other than an alarm clock (e.g., children, hobbies). Nonetheless, the µMCTQ also offers an advantage when compared with the stdMCTQ: it allows for the assessment of the circadian phase of people who mostly use alarm clocks on work-free days by asking them to consider only those work-free days on which they do not use an alarm clock. We use sleep behavior on free days as a proxy for chronotype because it is less confounded by social constraints and therefore is a closer reflection of entrained phase. Only for this conceptual reason, we usually do not compute MSF_{sc} when subjects report using alarm clocks on free days in the stdMCTQ (Pilz et al., 2018; Roenneberg et al., 2012; data from study 1). However, several studies have computed chronotype based on people who use an alarm clock on free days. While this is theoretically possible, we strongly recommend stating it clearly in the publication. Individuals who use alarm clocks on work-free days show slightly later mid-sleep and MSF_{sc} than subjects who do not (Suppl. Fig. S5).

Time Frames of the Questionnaires

The stdMCTQ has been used for more than 15 years in studies with varying research questions and designs. Originally, it asked people about their sleep behavior "in a regular week." Depending on the specific study design and question, the time frame assessed by the stdMCTQ has been modified to fit the demands of the investigation. Here, we suggest using 6 weeks with the µMCTQ to obtain a stable assessment that can still accommodate, for example, seasonal changes. stdMCTQ ("a regular week") and µMCTQ (past 6 weeks) in study 1 used different time frames for assessment but still corresponded well. Only the µMCTQ was used in study 2.

CONCLUDING REMARKS

We have developed and validated an ultra-short version of an already well-established instrument, the stdMCTQ. Both the stdMCTQ and the µMCTQ can be used to estimate PoE and can serve as good alternatives to time-consuming and more expensive measurements such as sleep logs, actimetry, and DLMO. They allow the calculation of quantitative, not qualitative, variables and thereby permit a range of statistical operations impossible to conduct with categorical data.

The µMCTQ, in alignment with the stdMCTQ, represents a valuable tool to assess information about the human clock in a concise manner. It uses relevant questions established by the stdMCTQ but might offer a better alternative for large samples and longer study durations, which would benefit from shorter questionnaires that offer relevant information about sleep-wake behavior.

ACKNOWLEDGMENTS

We would like to thank Marijke Gordijn for technical support with the melatonin assays and the participants for their time and willingness to participate. This study was financed in part by the Coordenação de Aperfeiçoamento de Pessoal de Nível Superior–Brasil (CAPES) Finance Code 001 (A046/2013–CAPES/PVE), the Deutscher Akademischer Austauschdienst (PROBRAL–CAPES/DAAD), as well as the FoeFoLe program at LMU (registration No. 37/2013).

AUTHOR CONTRIBUTIONS

T.R. and E.W. developed the µMCTQ. N.G., L.K.P., S.M., and T.R. designed the studies. L.K.P., N.G., D.L., and S.M. collected and organized the data for the µMCTQ validation and C.V., T.R., and E.W. did the same for the stdMCTQ validation. N.G., L.K.P., S.M., G.F., M.S., R.C., E.W., G.Z., C.V., and T.R. analyzed the data. N.G., L.K.P., S.M., and T.R. wrote the first draft of the article. All authors read, extensively revised, and approved the final article.

CONFLICT OF INTEREST STATEMENT

The authors have no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

ORCID iDs

Luísa K. Pilz https://orcid.org/0000-0001-7328-6204
Céline Vetter https://orcid.org/0000-0002-3752-1067
Marco Salamanca https://orcid.org/0000-0002-8113-3440

NOTE

Supplementary material is available for this article online.

REFERENCES

Benloucif S, Burgess HJ, Klerman EB, Lewy AJ, Middleton B, Murphy PJ, Parry BL, and Revell VL (2008) Measuring melatonin in humans. J Clin Sleep Med 4:66-69.

Bland JM and Altman DG. (1986) Statistical methods for assessing agreement between two methods of clinical measurement. Lancet 1(8476):307-10.

Bland JM and Altman DG (1999) Measuring agreement in method comparison studies. Stat Methods Med Res 8(2): 135-60.

Boyle GJ, Saklofske DH, and Matthews G (2015) Criteria for selection and evaluation of scales and measures. In: Boyle GH, Saklofske DH, and Matthews G, editors. *Measures of personality and social psychological constructs*. San Diego (CA): Academic Press. p. 3-15.

Braun R, Kath WL, Iwanaszko M, Kula-Eversole E, Abbott SM, Reid KJ, Zee PC, and Allada R (2018) Universal method for robust detection of circadian state from gene expression. Proc Natl Acad Sci 115:E9247-E9256.

Burgess HJ, Wyatt JK, Park M, and Fogg LF (2015) Home circadian phase assessments with measures of compliance yield accurate dim light melatonin onsets. Sleep 38:889-897.

Facer-Childs ER, Campos BM, Middleton B, Skene DJ, and Bagshaw AP (2019) Circadian phenotype impacts the brain's resting-state functional connectivity, attentional performance, and sleepiness. Sleep 42:pii:zsz033.

Goodwin LD and Leech NL (2006) Understanding correlation: factors that affect the size of *r*. J Exp Educ 74:249-266.

Horne JA and Ostberg O (1976) A self-assessment questionnaire to determine morningness-eveningness in human circadian rhythms. Int J Chronobiol 4:97-110.

Kantermann T and Eastman CI (2018) Circadian phase, circadian period and chronotype are reproducible over months. Chronobiol Int 35:280-288.

Kantermann T, Juda M, Merrow M, and Roenneberg T (2007) The human circadian clock's seasonal adjustment is disrupted by Daylight Saving Time. Curr Biol 17:1996-2000.

Kantermann T, Sung H, and Burgess HJ (2015) Comparing the Morningness-Eveningness Questionnaire and Munich ChronoType Questionnaire to the dim light melatonin onset. J Biol Rhythms 30:449-453.

Kitamura S, Hida A, Aritake S, Higuchi S, Enomoto M, Kato M, Vetter C, Roenneberg T, and Mishima K (2014) Validity of the Japanese version of the Munich ChronoType Questionnaire. Chronobiol Int 31:845-850.

Klerman EB, Gershengorn HB, Duffy JF, and Kronauer RE (2002) Comparisons of the variability of three markers of the human circadian pacemaker. J Biol Rhythms 17:181-193.

Kudielka BM, Broderick JE, and Kirschbaum C (2003) Compliance with saliva sampling protocols: electronic monitoring reveals invalid cortisol daytime profiles in noncompliant subjects. Psychosom Med 65:313-319.

Laing EE, Möller-Levet CS, Poh N, Santhi N, Archer SN, and Dijk D-J (2017) Blood transcriptome based biomarkers for human circadian phase. eLife 6:e20214.

Lewy AJ and Sack RL (1989) The dim light melatonin onset as a marker for circadian phase position. Chronobiol Int 6:93-102.

Pilz LK, Keller LK, Lenssen D, and Roenneberg T (2018) Time to rethink sleep quality: PSQI scores reflect sleep quality on workdays. Sleep 41.

Pullman RE, Roepke SE, and Duffy JF (2012) Laboratory validation of an in-home method for assessing circadian

phase using dim light melatonin onset (DLMO). Sleep Med 13:703-706.

Roenneberg T, Allebrandt KV, Merrow M, and Vetter C (2012) Social jetlag and obesity. Curr Biol 22:939-943.

Roenneberg T, Daan S, and Merrow M (2003a) The art of entrainment. J Biol Rhythms 18:183-194.

Roenneberg T, Keller LK, Fischer D, Matera JL, Vetter C, and Winnebeck EC (2015) Human activity and rest in situ. Methods Enzymol 552:257-283.

Roenneberg T, Kuehnle T, Juda M, Kantermann T, Allebrandt K, Gordijn M, and Merrow M (2007a) Epidemiology of the human circadian clock. Sleep Med Rev 11:429-438.

Roenneberg T, Kumar CJ, and Merrow M (2007b) The human circadian clock entrains to sun time. Curr Biol 17:R44-R45.

Roenneberg T, Wirz-Justice A, and Merrow M (2003b) Life between clocks: daily temporal patterns of human chronotypes. J Biol Rhythms 18:80-90.

Ryu H, Joo EY, Choi SJ, and Suh S (2018) Validation of the Munich ChronoType Questionnaire in Korean older adults. Psychiatry Investig 15:775-782.

Stothard ER, McHill AW, Depner CM, Birks BR, Moehlman TM, Ritchie HK, Guzzetti JR, Chinoy ED, LeBourgeois MK, Axelsson J, et al. (2017) Circadian entrainment to the natural light-dark cycle across seasons and the weekend. Curr Biol 27:508-513.

Swaminathan K, Klerman EB, and Phillips AJK (2017) Are individual differences in sleep and circadian timing amplified by use of artificial light sources? J Biol Rhythms 32:165-176.

Wickham H (2016). ggplot2: Elegant Graphics for Data Analysis. New York: Springer-Verlag.

Wittenbrink N, Ananthasubramaniam B, Münch M, Koller B, Maier B, Weschke C, Bes F, de Zeeuw J, Nowozin C, Wahnschaffe A, et al. (2018) High-accuracy determination of internal circadian time from a single blood sample. J Clin Invest 128:3826-3839.

Wright KP, McHill AW, Birks BR, Griffin BR, Rusterholz T, and Chinoy ED (2013) Entrainment of the human circadian clock to the natural light-dark cycle. Curr Biol 23:1554-1558.

6. Paper II

Chronotype, Social Jetlag, and Nicotine Use

Neda Ghotbi[*,†], Andrea Rabenstein[‡], Luísa K. Pilz[§,||], Tobias Rüther[‡,1] and Till Roenneberg[*,1,2]

[*]*Institute of Medical Psychology, LMU Munich, Munich, Germany,* [†]*Department of Child and Adolescent Psychiatry, Psychotherapy and Psychosomatics, University Hospital, LMU Munich, Munich, Germany,* [‡]*Department of Psychiatry and Psychotherapy, University Hospital, LMU Munich, Munich, Germany,* [§]*Laboratório de Cronobiologia e Sono, Hospital de Clínicas de Porto Alegre, Universidade Federal do Rio Grande do Sul, Porto Alegre, Brazil, and* [||]*Graduate Program in Psychiatry and Behavioral Sciences, Universidade Federal do Rio Grande do Sul, Porto Alegre, Brazil*

Abstract Late chronotype, which often leads to higher social jetlag (SJL), is strongly associated with the prevalence of smoking. Any circadian disruption, strain, or misalignment, results in people not being able to live according to their biological time as is described by SJL, which we will therefore use as umbrella term. We hypothesized two scenarios potentially explaining the association between smoking and SJL: (A) If smoking delays the clock, circadian phase should advance upon quitting. (B) If people smoke more to compensate the consequences of SJL, circadian phase should not change upon quitting. To distinguish between these two hypotheses, we accompanied participants of a smoking cessation program (not involving nicotine replacement products) across the cessation intervention (3 weeks prior and 6 weeks after) by monitoring their circadian behavior, sleep quality, and daytime sleepiness via questionnaires and actimetry. Our results show no effects of cessation on SJL, chronotype, sleep quality, or daytime sleepiness, thereby favoring scenario (B). Thus, smoking may be a consequence of rather than a cause for SJL. Daytime sleepiness was a significant predictor for the outcome in our model but did not improve with cessation.

Keywords cessation, sleep, owls, larks, addiction

Despite further declines in global tobacco use, the World Health Organization (WHO) estimated in their latest 2019 report rising numbers of tobacco-consumption-related diseases and deaths. Considering these prolonged effects and that a projected 17.1% of the world's population will still smoke in 2025, the importance of investigating effects of smoking and expanding our knowledge on successful cessation cannot be stressed enough (WHO, 2019). Our study contributes to this by further investigating the relationship between smoking and circadian sleep-wake behavior. Previous studies reported a higher prevalence of smoking among late chronotypes, that is, people whose circadian clocks synchronize late in reference to the light-dark cycle (Adan, 1994; Antypa et al., 2016; Fabbian et al., 2016; Kwon and Lee, 2022; Suh et al., 2017; Wittmann et al., 2006). In these studies, chronotype was assessed either via the Munich Chronotype Questionnaire (MCTQ), which

1. Authors contributed equally.

2. To whom all correspondence should be addressed: Till Roenneberg, Institute of Medical Psychology, LMU Munich, Goethestrasse 31, D-80336 Munich, Germany; e-mail: roenneberg@lmu.de.

JOURNAL OF BIOLOGICAL RHYTHMS, Vol. XX No. X, Month 202X 1–15
DOI: 10.1177/07487304231177197

evaluates chronotype as the phase-relationship between individual circadian system and signals of the cyclic environment (zeitgebers) (Roenneberg et al., 2003), or the Morningness-Eveningness-Questionnaire, which is a psychological assessment of diurnal preference (Horne and Ostberg, 1976). Lower sleep quality and disrupted sleep architecture have also been reported in smokers (Hu et al., 2007; Jaehne et al., 2012; Phillips and Danner, 1995; Wetter and Young, 1994).

The human clock actively synchronizes to specific *zeitgebers*, of which light is the predominant one for most organisms, including humans (Duffy and Wright, 2005; Roenneberg et al., 2007; Wright et al., 2013). The phase-relationship between the circadian clock and the *zeitgeber* is called phase of entrainment (PoE). In humans, this PoE is often called "chronotype," which is almost normally distributed in populations, varies between people and conditions and ranges from extreme early chronotypes ("larks") to extreme late chronotypes ("owls"). The timing of most functions is aligned with chronotype, including the timing of sleep (Roenneberg et al., 2007).

Chronotype has been discussed as a psychological trait (i.e. independent of situational effects) (Steyer et al., 1992), assessible by measuring diurnal preferences (Horne and Ostberg, 1976). Human clocks under real-life conditions, however, often face greatly varying entrainment conditions and are able to adapt. We therefore view chronotype as a biological state-trait-interaction. We regard chronotype as a surrogate for PoE. Like PoE, chronotype dynamically adapts to external *zeitgeber* cycles and reflects the entire organism's overall temporal organization under entrained conditions. The variation of these conditions contributes to the variance in chronotype, as do genes and age (Roenneberg et al., 2019).

Modern lifestyle deprives people of both natural light during the day (e.g. by mostly living indoors) and darkness during the night (use of artificial light) (Roenneberg et al., 2003). The strength of light as a *zeitgeber* has therefore drastically decreased, thereby delaying most chronotypes (with the exception of extreme larks) and increasing the gap between larks and owls (Wright et al., 2013). The increasing mismatch between the internal and external clock has become a stressor for the majority of the population (Roenneberg et al., 2015), leads to so-called social jetlag (SJL) and consequently to sleep debt over the course of the workweek, which is often compensated for on weekends (Wittmann et al., 2006). Here, we use the umbrella term SJL for all kinds of circadian disruptions, misalignments, mismatches, or strains.

Suffering from chronic SJL is associated with numerous health risk factors, for example, increased risk of metabolic illness, depressive symptoms, and addiction behavior (Antypa et al., 2016; Broms et al., 2012; Levandovski et al., 2011; Parsons et al., 2015; Roenneberg et al., 2012). The strong positive correlation between SJL and the probability of being a smoker (Wittmann et al., 2006) is of particular interest for our investigation, but we do not know whether smoking delays the circadian clock, thereby increasing SJL, or whether SJL fosters smoking, for example as a coping strategy.

We followed people through the process of quitting smoking without nicotine replacement therapy, while measuring behavioral outputs of the clock before and after cessation to compare potential effects of tobacco abstinence. We hypothesized that if smoking delays the clock, people's circadian phase should advance when they stop (A). If people remained the same chronotype after quitting, the second alternative (B), smoking to compensate for consequences of SJL, would be more likely.

METHODS

Design and Cohort

Study Design. Participants of a smoking cessation program at the Tobacco Outpatient Clinic of the Psychiatric Clinic at the LMU Munich were recruited through newspaper advertisement and the LMU online newsletter between October 2014 and March 2016. The course consisted of six weekly group appointments and was based on the *smoke free* manual developed by the Institute for Therapy Research in Munich (IFT) (Kröger and Gradl, 2007; Kufeld and Bühringer, 2010). The manual determines that the group will try to quit smoking collectively at the week 4 meeting of participation. After the course, participants were monitored for three more weeks (total investigation period: 9 weeks). During the sixth and seventh week, subjects engaged in two phone interviews carried out by the study team. A final group appointment was scheduled at the end of the ninth week (appointment 9).

Several measurements were taken during the first and last appointment: questionnaires regarding chronotype, sleep habits and quality, tobacco dependency, and smoking habits. Subjects were given actimeters for continuous measurement of their activity (9 weeks). At each appointment, expiratory carbon monoxide (eCO) levels were assessed, and the Nicotine Use Inventory (NUI) Questionnaire was filled in by the subject. The NUI was also administered by the study team during phone interviews (appointment 7 & 8). The time period before the cessation intervention is called T0, while the period of time after the intervention is called T1 (see Figure 1 for more detail).

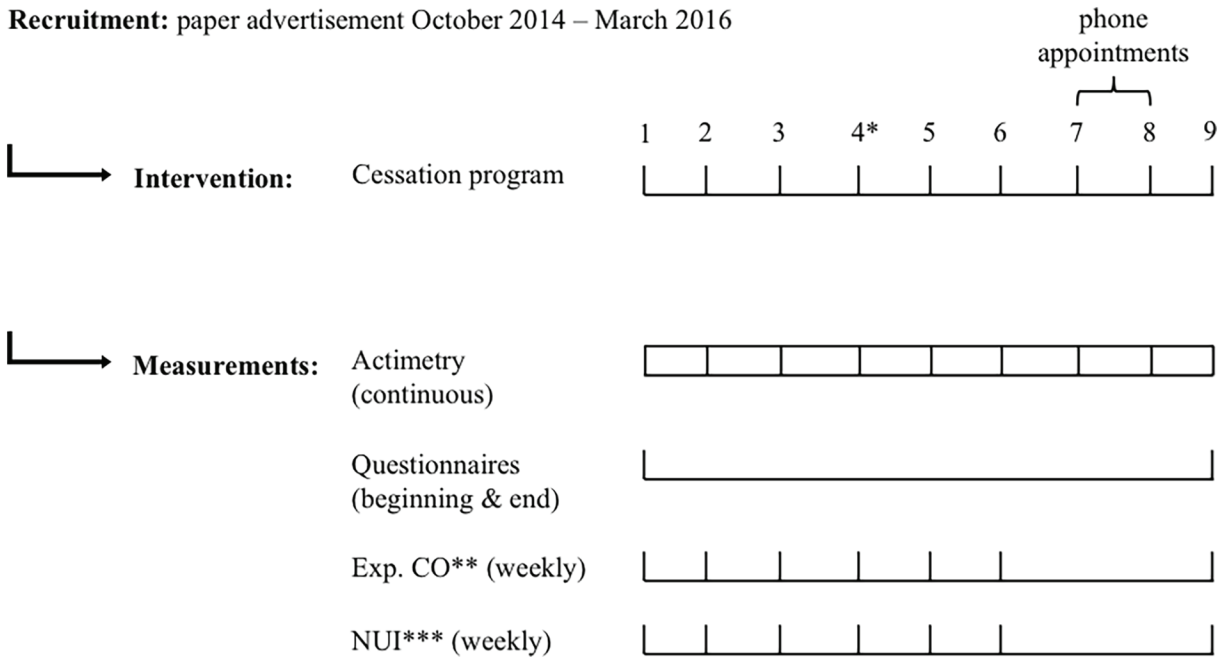


Figure 1. Study design. * = Day of quitting, ** = eCO (expiratory CO) levels measured weekly except for week 7 and 8, * = Nicotine Use Inventory (NUI) administered weekly at group or phone appointment. Forty-nine subjects completed the study, total duration of study = 9 weeks, duration of cessation program = 6 weeks, phone interviews in week 7 and 8. Continuous monitoring of locomotor activity via actimetry: 9 weeks. All questionnaires (except for the NUI) were administered once at the beginning and once at the end of the study. Expiratory CO measured at the end of every appointment; NUI administered at every appointment.**

All participants gave their informed, written consent. The study was approved by the Ethics Committee of the LMU (approval #508-14) and conducted in accordance with the Declaration of Helsinki.

Criteria and Sample Size. An a priori power analysis was performed using G*Power3 to determine the required sample size (*t*-test to test the difference between two dependent means, two-tailed) (Faul et al., 2007, 2009). Alpha was set to .05. With an effect size of $d = 0.5$, the sample size was 54, while with an effect size of $d = 0.6$, the required sample size was 39. We therefore aimed to recruit between 39 and 54 participants.

Our exclusion criteria were shift-workers and individuals with other nonstandard weekly schedule (i.e. five workdays and two work-free days), patients diagnosed with a psychiatric or neurological illness (other than tobacco use disorder), individuals who came back from a trans-meridian flight 3 months prior to participation.

Time Changes. The following time changes occurred during our study: 21 participants went into daylight saving time (DST). Twelve participants extended with their last 2 days into DST (questionnaires were administered before the transition weekend and the hanging days were excluded from activity recordings). Nine participants were recorded for 5 weeks in standard time (ST) and 4 weeks in DST; six subjects spent 2 weeks in DST and 7 weeks in ST. In these cases, we excluded 7 days after the time change from activity recordings. Included data are expressed in local time. We conducted the analysis both with corrected (=adjusted to local time) and uncorrected data, which had no effect on the results regarding direction and significance. We therefore conclude that our observations are not due to DST-related corrections. Here, we report results produced with corrected data.

Abstinence. Abstinence was defined as stating not to have smoked during the past 7 days on each NUI and eCO-levels ≤ 5 ppm, indicating a verification of the self-reports (Middleton and Morice, 2000; Javors et al., 2005; Kapusta et al., 2010; West et al., 2005; Patrick et al., 1994). Subjects with eCO-values > 5 ppm and/or self-reported smoking were assigned to the so called "continue" group, while those who met abstinence criteria were assigned to the so called "quit" group.

Interventions and Measurements

Cessation Program. The *smoke free* manual uses elements of cognitive behavioral therapy and motivational therapy (Kröger and Gradl, 2007). Concepts of

Table 1. Sample characteristics.

	All participants, *n*	%	Quit group, *n*	%	Continue group, *n*	%	Dropouts, *n*
Total	49		22		27		2
Female	32	65.31	14	63.64	18	66.67	2
Male	17	34.69	8	36.36	9	33.33	0
Average age ± SD	46.02 ± 12.16		45.91 ± 11.40		46.11 ± 12.97		56.00 ± 4.24
Age range	23-69		23-69		25-69		53-59
Primary-level education[a]	9	18.37	4	18.18	5	18.52	
Secondary-level education[a]	40	81.63	18	81.82	22	81.48	
Single/separated/divorced/widowed	28	57.14	12	54.55	16	59.26	
Married/partnership	21	42.86	10	45.45	11	40.74	
Smoke-free environment T0[b]	35	71.43	14	63.64	21	77.78	
Not smoke-free environment T0	14	28.57	8	36.36	6	22.22	
Smoke-free environment T1[b]	38	77.55	18	81.82	20	74.07	
Not smoke-free environment T1	9	18.37	4	18.18	5	18.52	
Fagerström T0							
0-2			3	13.64	4	14.81	
3-5			13	59.09	19	70.37	
6-7			5	22.73	3	11.11	
8-10			1	4.55	1	3.7	
Fagerström T1							
0-2			22	100.00	11	40.74	
3-5			—	—	9	33.33	
6-7			—	—	3	11.11	
8-10			—	—	—	—	

[a]Primary-level education at German school level included the following categories: attended primary school (Hauptschule) or dropped out. Secondary-level education at German school level included: higher secondary school (Gymnasium), lower secondary school (Realschule). [b]T0 = before planned cessation, T1 = after planned cessation.

behavioral therapy, especially in the group setting, have been shown to be effective in smoking cessation (Stead et al., 2017).

Actimetry. The actimeter is a wrist-worn device, measuring locomotor activity via an integrated accelerometer. The devices (Daqtometers by Daqtix GmbH) were worn continuously for the total study duration. Activity was recorded at 1 Hz; the average activity counts stored every 30 sec, and data were averaged into 10 min bins for further analyses. These data give insight into the daily phase of general locomotor activity using the ChronoSapiens-software (Chronsulting UG) (Roenneberg et al., 2015). The acrophase of the daily activity profiles (maximum of 1-harmonic, 24 h cosine fit; abbreviated here as "Phi": ψ_{act}) representing activity's daily "center of gravity." We excluded days from the analysis that contained more than 1 h of missing data. For the analysis of predictability of outcome via ψ_{act}, daily ψ_{act} values were averaged across 3-week sections in each individual, resulting in $\psi_{act\text{-}pre}$ for weeks 1 to 3 (prior to cessation), $\psi_{act\text{-}cess}$ for weeks 4 to 6 and $\psi_{act\text{-}post}$ for weeks 7 to 9 (both postcessation) per subject. For analysis of associations between number of smoked cigarettes and actimetry data, the daily ψ_{act} values were averaged across each week in each individual, resulting in the variable $\psi_{act\text{-}week}$. Data are expressed in local time.

Questionnaires

Demographic Data/General Questionnaire. Participants filled in a general questionnaire for demographic data, assessing personal and educational information, smoking method (e.g. pre-manufactured or hand-rolled cigarettes) and stimulant use (caffeine/alcohol consumption, psycho-/neuropharmacological medication; yes- or no-answers) (Table 1).

Munich Chronotype Questionnaire. The MCTQ was developed by Roenneberg et al. (2003) and asks simple questions about sleep-wake behavior separately for work- and work-free days. It has been validated in various studies against actimetry and biochemical measurements of the circadian clock (Kantermann et al., 2015; Kitamura et al., 2014; Pilz et al., 2018). The MCTQ has been used since the year 2003, thus generating large amounts of valuable information on individuals' sleep-wake behavior (the MCTQ database currently comprises close to 300.000 entries and was used in this study to compare sample and population

data). It uses sleep timing to approximate the circadian state or chronotype of an individual. Work-free days are considered to be affected less by constraints on sleep timing due to specific schedules or social demands. Therefore, the midpoint between sleep onset and sleep end on a work-free day, further corrected for possible sleep debt accumulated during the workweek, is calculated to represent chronotype (MSF_{sc}). In this study, the MSF_{sc} was only calculated when the subject did not use an alarm clock, since MSF_{sc} calculation relies on having free days, which are not spent according to given (work-) schedules. SJL describes the difference of sleep timing between work and work-free days (MSF – MSW). We used the standard German version. Data are expressed in local time. More information on the MCTQ is available at: http://thewep.org/documentations/mctq.

Pittsburgh Sleep Quality Index. The Pittsburgh Sleep Quality Index (PSQI) has been validated in multiple studies (Buysse et al., 1989; Carpenter and Andrykowski, 1998; Grandner et al., 2006; Mollayeva et al., 2016). Subjects report on and rate their subjective sleep quality over the last 4 weeks, report on daytime sleepiness and specify use of sleep medication. Addition of component scores, generates an overall score ranging from 0 to 21 points with higher scores indicating worse sleep quality. The general cut-off separating good from poor sleep quality is set at >5.

Epworth Sleepiness Scale. The Epworth Sleepiness Scale (ESS) was developed in 1991 and updated in 1997 (the updated version was used here) (M. Johns and Hocking, 1997; M. W. Johns, 1991, 1992). Subjects are asked to rate their usual chances of dozing off or falling asleep while engaged in different activities. The ESS score (sum of all item scores) ranges from 0 to 24. The higher the score, the higher the probability and extend of daytime sleepiness. Global ESS scores above 5 indicate higher daytime sleepiness and scores above 10 indicate excessive daytime sleepiness.

Nicotine Use Inventory. The NUI has previously been used to assess continuous nicotine abstinence (Tonstad et al., 2006; Koegelenberg et al., 2014). Five initial questions assess the consumption of cigarettes and other nicotine containing products during the past 7 days (yes-/no-answers). The last two questions assess the quantity of smoked cigarettes through free text answers. We used the NUI to determine successful smoking cessation in addition to eCO measurements. If participants answered questions 1 through 4 with "no" and question 7 with "0," it was used as evidence of self-reported nicotine abstinence of the past 7 days. Any other answers on the NUI indicated that the subject had smoked or been exposed to nicotine (see section on abstinence for more detail). The estimated amount of weekly consumption was generated through multiplication ($\times 7$) of the average daily number of smoked cigarettes derived from the weekly NUI. The full German NUI and an English translation are provided in the Supplementary Material.

Expiratory Carbon Monoxide Measurements (eCO Measurements)

The expiratory carbon monoxide levels (in parts per million/ppm) were measured at each weekly personal appointment using the Bedfont EC50-MICRO CO monitor smokerlyser (Bedfont Instruments; Kent, United Kingdom). These eCO levels were used, along with NUI results, to determine abstinence since eCO levels have been reported to correlate well with the number of smoked cigarettes (Deveci et al., 2004). Ambient CO-levels were assessed before the measurements and ranged between 0 and 3 ppm.

Assessment Dim Light Melatonin Onset

Dim Light Melatonin Onset (DLMO) is a gold-standard for measuring the timing of synchronization via a biological marker. Therefore, multiple saliva samples to measure melatonin and assess DLMO were gathered from every subject once during T0 (week 2) and once during T1 (week 9). Participants were instructed to self-collect hourly samples at home. Unfortunately, the samples were not analyzable due to two main problems: (1) many participants were not able to collect sufficient amounts of saliva using the salivettes and lower salivary flow rates in smokers compared to nonsmokers have been reported (Rad et al., 2010) and (2) due to a freezer breakdown in our laboratory the majority of samples was lost.

Statistical Analysis

Statistical analyses were performed using R, SPSS Statistics 26 & 27 and Excel 2011 & 2018 for Macintosh. Figures were generated using Prism 8 and R using the package *ggplot2* (Wickham et al., 2016).

Statistical Hypotheses Tests. Based on the distribution of variables, which was assessed via Shapiro-Wilk tests and visual inspection of histograms, statistical hypotheses tests were chosen to compare questionnaire data in the respective samples and between time points (Hinkle et al., 2003). The Wilcoxon signed rank test was used to compare related sample

variables and the Mann-Whitney *U*-test for unrelated sample variables. Nonparametric tests were chosen because the distribution of variables was largely non-normal. The Wilcoxon signed rank test was performed on subjects with complete data. Therefore, when data were lost during follow-up, the case was excluded (MCTQ: five participants of continue group were lost to follow-up, ESS & PSQI: four participants of continue group were lost to follow-up). The alpha-level was set to 0.05 and, due to multiple testing, the Bonferroni correction was applied, leading to new significance levels: for MSFsc, SJL, PSQI and ESS = 0.01 (Abdi, 2007; Noble, 2009).

Generalized Estimating Equations. To account for the longitudinal data (time point and continuous data), we used Generalized Estimating Equation (GEE) models with a logit link function and an unstructured matrix (Liang and Zeger, 1986).

We used GEE to investigate the relationship of cessation status (during T0 & T1) and ψ_{act} and results from the administered questionnaires. GEE was also used to test the predictability of cessation status by ψ_{act} (during T0 and T1). ψ_{act} values, along with age and sex, were tested as predictors of the outcome (successful cessation or continuing to smoke)—called "group." Results were controlled for age, sex, smoking method, and stimulants, the pre-post study design was also considered in the model. The distribution was specified as binomial regarding outcome analyses. Potential effects of group or time point as well as interaction effects of group and time point in regard to (possible changes in) questionnaire data, while controlling for age, sex, smoking method, and stimulant use were also examined via GEE. Variables were coded as follows: quit group = 0, continue group = 1, male = 0, female = 1, T0 = 0, T1 = 1. Caffeine: yes = 1, no = 0; alcohol: yes = 1, no = 0, medication: yes = 1, no = 0, premanufactured cigarettes = 0, hand-rolled cigarettes = 1. All other included variables are continuous.

Binary Logistic Regression. To investigate the predictability of outcome by noncontinuous data, such as questionnaire variables (MSF_{sc}, SJL, PSQI, and ESS overall scores), number of smoked cigarettes, age, sex, smoking method, and stimulant use, we conducted a binary logistic regression analysis. MSF_{sc} and SJL, as well as overall PSQI and ESS scores (each during T0 and T1) were tested. Variables were coded as follows: male = 0, female = 1, quit group = 0, continue group = 1, T0 = 0, and T1 = 1. Stimulant use (further specified for substance): yes = 1, no = 0, premanufactured cigarettes = 0, hand-rolled cigarettes = 1. All other variables are continuous.

RESULTS

Sample Characteristics

We recruited 51 subjects for this study: 2 participants withdrew after the first appointment and 49 subjects completed the study (in separate groups, 3-12 participants at a time). Their age ranged from 23 to 69 years (median = 47.00), and the cohort consisted of 32 women and 17 men.

On average (mean ± SD), participants scored 4.47 ± 1.84 in the Fagerström Test for Nicotine Dependence (FTND), smoked 16 ± 6 cigarettes/day and had been smoking for 27 ± 11.86 years. Almost 80% of participants smoked premanufactured cigarettes, while the rest hand-rolled them. The majority of participants reported having tried to quit smoking before (47 of 49) but except for one participant, without supervision. Other participants had used self-help literature (38.78%) or nicotine replacement products (24.49%). None of the participants took neuro- or psychopharmacological medication. Caffeine (coffee and caffeinated drinks) and alcohol intake were assessed as occurring regularly over the past 4 weeks (yes-/no-answers: 76.4% drank caffeine regularly, 67.3% drank alcohol regularly). More detailed sample characteristics can be obtained from Table 1.

Participants who successfully quit smoking during the program and remained abstinent to the end of the study (no relapses or grace period) form the "quit" group (45%), while the rest form the "continue" group (55%). Data on sociodemographic characteristics of both groups are shown in Table 1. Age, sex, and educational level were similar across groups.

Sufficient data to calculate the different ψ_{act} for all the 3-week periods was available in 38 participants (25 female, age range: 23-69 years, age mean ± SD: 44.79 ± 12.52, successful cessation in 19 participants).

Complete questionnaire data were available in 44 participants (30 female, age range: 23-69 years, age mean ± SD: 45.64 ± 12.63, successful cessation in 22 participants).

Continuous and Discrete Time Point Data Comparisons

For comparison between the two time points as well as between groups, MSF_{sc} and SJL (MCTQ), PSQI and ESS overall scores were investigated using either the Wilcoxon signed rank test or the Mann-Whitney *U*-test. All results were non-significant (for more detail, see Figures 2-5 for MSF_{sc}, SJL, PSQI, and ESS scores and Supplementary Table S1 for detailed calculations on all variables).

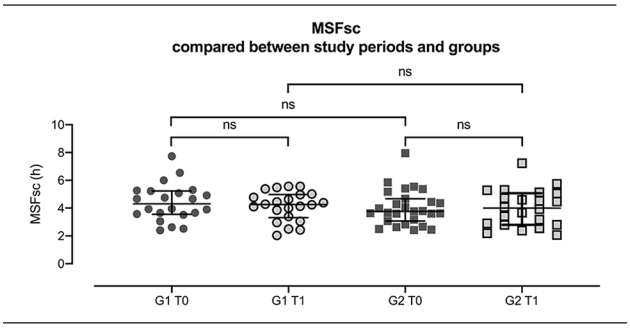


Figure 2. MSF_{sc} **compared between study periods and groups. G1 = quit group, G2 = continue group, T0 = before attempt at cessation, T1 = after attempt at cessation. Each data point represents an individual result. Error bars indicate interquartile range Q1-Q3. Variables in the continue group during T0 follow a normal distribution; all other variables are not normally distributed. Comparisons of MSFsc during T0 and T1 within and across groups: MSFsc quit group during T0 and T1 Wilcoxon signed-rank test: $p = 0.158$, $N = 22$. MSFsc continue group during T0 and T1. Wilcoxon signed-rank test: $p = 0.884$, $N = 22$. MSFsc of both groups during T0. Mann-Whitney *U*-test: $p = 0.345$. MSFsc of both groups during T1. Mann-Whitney *U*-test: $p = 0.606$. Abbreviation: MSFsc = mid-sleep on free days corrected for sleep debt.**

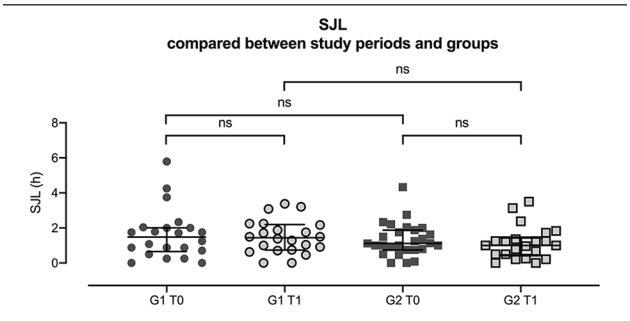


Figure 3. SJL compared between study periods and groups. G1 = quit group, G2 = continue group, T0 = before attempt at cessation, T1 = after attempt at cessation. Each data point represents an individual result. Error bars indicate interquartile range Q1-Q3. Variables in the continue group during T0 follow a normal distribution; all other variables are not normally distributed. Comparisons of SJL during T0 and T1 within and across group: SJL of quit group during T0 and T1. Wilcoxon signed-rank test: $p = 0.931$, $N = 22$. SJL of continue group during T0 and T1. Wilcoxon signed-rank test: $p = 0.171$, $N = 22$. SJL of both groups during T0. Mann-Whitney *U*-test: $p = 0.673$. SJL of both groups during T1. Mann-Whitney *U*-test: $p = 0.159$. Abbreviation: SJL = social jetlag.

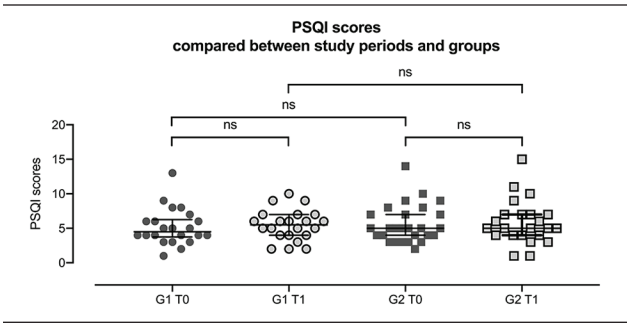


Figure 4. PSQI overall scores compared between study periods and groups. G1 = quit group, G2 = continue group, T0 = before attempt at cessation, T1 = after attempt at cessation. Each data point represents an individual result. Error bars indicate interquartile range Q1-Q3. Variables in continue group during T0 are normally distributed, all other variables are not normally distributed. Comparison of PSQI results during T0 and T1 within and across groups: PSQI scores of quit group during T0 and T1. Wilcoxon signed-rank test: $p = 0.468$, $N = 22$. PSQI scores of continue group during T0 and T1. Wilcoxon signed-rank test: $p = 0.967$; $N = 23$. PSQI results of both groups during T0. Mann-Whitney *U*-test: $p = 0.563$. PSQI results of broth groups during T1. Mann-Whitney *U*-test: $p = 0.936$. Abbreviation: PSQI = Pittsburgh Sleep Quality Index.

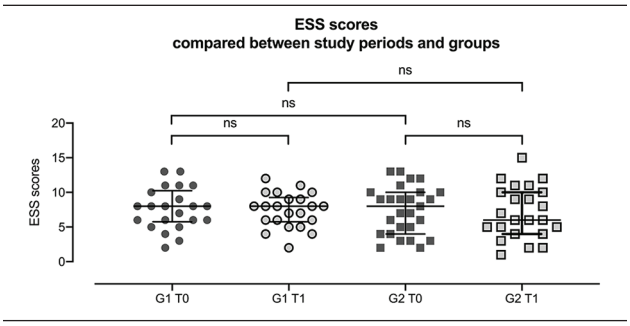


Figure 5. ESS overall scores compared between study periods and groups. G1 = quit group, G2 = continue group, T0 = before attempt at cessation, T1 = after attempt at cessation. Each data point represents an individual result. Error bars indicate interquartile range Q1-Q3. All variables follow a not normal distribution. Comparison of ESS scores at T0 and T1 within and across group: ESS scores of quit group during T0 and T1. Wilcoxon signed-rank test: $p = 0.896$, $N = 22$. ESS scores of continue group during T0 and T1. Wilcoxon signed-rank test: $p = 0.909$, $N = 23$. ESS results of both groups during T0. Mann-Whitney *U*-test: $p = 0.841$. ESS results of both groups during T1. Mann-Whitney *U*-test: $p = 0.665$. Abbreviation: ESS = Epworth Sleepiness Scale.

Individual values and their trajectories (and corresponding percentages) of MSF_{sc} and SJL were calculated whenever MCTQ data were available both at T0 and T1. The distribution and direction of changes (advanced or delayed $MSF_{sc;}$ increase or decrease of SJL) was largely even across the groups. Calculated effect sizes, regarding the differences between time points for MSF_{sc} and SJL in the two groups separately, were small. About 56.82% of all participants advanced their MSF_{sc}, while the others delayed. The overall average advance equaled about 6 minutes (Mean ± SD: −0.11 ± 0.76 h; range: −2.16 to 2.08 h). About 52.27% showed a decrease in SJL, which on average was about 9 minutes (Mean ± SD: −0.16 ± 0.72 h; range: −2.58 to 1.00 h). In the quit group, 14 subjects (63.63 %) showed an advance of MSF_{sc} from T0 to T1, while 8 subjects delayed (effect size MSF_{sc} quit group, T1-T0: $d = -0.37$). Eleven successful (50.00 %) participants decreased in SJL, while 10 showed an increase in SJL values and 1 participant

Table 2. GEE Analysis: prediction of cessation status and relationships between variables.[a]

Test	β	OR	SE	95% CI of OR	*p*	QICC
Prediction of cessation status by (. . .)						61.39
age	−0.02	0.978	0.030	[0.92-1.04]	.457	
sex	−0.62	0.541	0.771	[0.12-2.45]	.426	
$\psi_{act\text{-}pre}$ week 1 -3	−0.05	0.953	0.314	[0.52-1.76]	.879	
$\psi_{act\text{-}cess}$ week 4 -6	−0.13	0.875	0.493	[0.33-2.30]	.786	
Relationship between ψ_{act} and (. . .)						231,82
cessation status	−0.60	0.551	0.442	[0.23-1.31]	.177	
age	−0.03	0.968	0.015	[0.94-0.99]	**.029***	
sex	−0.71	0.491	0.466	[0.20-1.22]	.127	
Relationship between MSF_{sc} and (. . .)						98.61
cessation status	0.16	1.175	0.301	[0.65-2.12]	.592	
age	−0.04	0.965	0.012	[0.94-0.99]	**.003****	
sex	−0.19	0.824	0.295	[0.46-1.47]	.510	
SJL	0.51	1.662	0.128	[1.29-2.13]	**<.001*****	
Relationship between SJL and (. . .)						88.89
cessation status	0.19	1.207	0.248	[0.73-1.99]	.461	
age	−0.002	0.998	0.012	[0.97-1.02]	.837	
sex	−0.19	1.211	0.267	[0.72-2.04]	.474	
MSF_{sc}	0.45	1.567	0.147	[1.18-2.09]	**.002****	
Relationship between PSQI and (. . .)						618.71
cessation status	−0.48	0.517	0.676	[0.16-2.32]	.476	
age	0.05	1.055	0.036	[0.98-1.13]	.135	
sex	−0.13	0.875	0.658	[0.24-3.18]	.840	
ESS score	0.04	1.042	0.080	[0.89-1.22]	.604	
Relationship between ESS and (. . .)						884.44
cessation status	0.36	1.440	0.814	[0.29-7.11]	.654	
age	0.01	1.006	0.031	[0.95-1.07]	.832	
sex	−1.13	0.324	0.883	[0.06-1.83]	.203	
PSQI score	0.03	1.036	0.140	[0.79-1.36]	.800	

Unstructured correlation matrix. Abbreviations: OR = odds ratio; SE = standard error; CI = confidence interval; QICC = corrected quasi likelihood under independence model criterion; PSQI = Pittsburgh Sleep Quality Index; ESS = Epworth Sleepiness Scale; MSFsc = mid-sleep on free days corrected for sleep debt; SJL = social jetlag..

[a]The model was additionally adjusted for caffeine-, alcohol-consumption and smoking method (premanufactured or hand-rolled cigarettes). Significant predictions and relationships: Prediction of cessation status by age (p = .029). Relationship between MSFsc and age (p = .003). Relationship between MSFsc and SJL (p = <.001). Relationship between SJL and MSFsc (p = .002).

*$p \leq 0.05$, **$p \leq 0.01$, ***$p \leq 0.001$, Bonferroni correction.

showed no SJL changes (effect size SJL quit group, T1-T0: $d = -0.15$). In the continue group, 11 subjects (50.00%) showed an advance of MSF_{sc}, which was counterbalanced by 11 subjects who delayed (effect size MSF_{sc} continue group, T1-T0: $d = 0.05$). In terms of SJL, 12 subjects (54.54 %) showed decreasing SJL values, while seven increased and SJL in three subjects remained unchanged (effect size SJL continue group, T1-T0: $d = -0.35$). Questionnaire data were insufficient for trajectory calculation in five members of the continue group.

The GEE analysis (controlled for age, sex, caffeine, alcohol, smoking method), revealed no effects of cessation status on actimetry or questionnaire data, which showed no significant differences over the investigation periods (pre-cess-post). Phase of activity (ψ_{act})—measured prior to the intervention—also did not predict cessation success (for detailed results see Table 2). We further used the GEE approach to probe whether there were effects of group or time point as well as interaction effects of group*time point regarding questionnaire results (MSFsc, SJL or PSQI and ESS scores). A significant interaction would suggest different trajectories between groups in the questionnaire outcomes. There was no significant effect of group, time point, or group*time point detectable (detailed results can be found in Supplemental Table S3 and Supplemental Figures S1-S4). Both MSFsc and ψ_{act} were significantly associated to age ($p < 0.05$). The model revealed associations of both MSFsc and ψ_{act} to age ($p < 0.05$) and associations between chronotype (MSFsc) and SJL (MSFsc = f (SJL): $p < 0.001$, SJL = f (MSFsc): $p < 0.05$) across investigation periods.

Prediction of Outcome

Binary logistic regression analysis was performed, testing whether cessation success could be predicted

Table 3. Binary logistic regression analysis of outcome prediction and model evaluation.[a]

Predictor	β	SE β	Wald χ^2	*df*	*p*	OR	CI for OR
MSF_{sc} T0[b]	−.252	.275	.845	1	.358	.777	.454-1.331
Sex[c]	−.089	.739	.015	1	.904	.914	.215-3.895
Constant	1.427	2.324	.377	1	.539	4.167	
SJL T0	−.142	.293	.296	1	.627	.867	.489-1.540
Sex	−.142	.745	.036	1	.849	.867	.201-3.739
Constant	.441	1.935	.052	1	.820	1.55	
ESS T0	−.336	.145	5.370	1	**.020***	.715	.538-.950
Age	−.022	.034	.411	1	.521	.979	.916-1.045
Sex	−.893	.875	1.043	1	.307	.409	.074-2.273
Constant	2.538	2.067	1.504	1	.220	12.615	
PSQI T0	.125	.128	.943	1	.331	1.133	.881-1.457
Age	−.019	.030	.395	1	.530	.981	.926-1.041
Sex	.066	.779	.007	1	.933	1.068	.232-4.917
Constant	−.292	1.635	.032	1	.858	.747	
No. of cigarettes T0	.003	.057	.002	1	.962	1.003	.896-1.122
Age	−.011	.028	.164	1	.686	.989	.937-1.044
Constant	.003	1.567	.000	1	.998	1.003	

Abbreviations: ESS = Epworth Sleepiness Scale; PSQI = Pittsburgh Sleep Quality Index; SE = standard error; ***df*** = degrees of freedom; OR = odds ratio; CI = confidence interval; SJL = social jetlag; MSFsc = mid-sleep on free days corrected for sleep debt.
Significant prediction of cessation status by ESS value at T0 (p = .020).
[a]The model was additionally adjusted for caffeine-, alcohol-consumption, and smoking method (premanufactured or hand-rolled cigarettes). Continue group coded as (=1), quit group (=0).
[b]T0 = before planned cessation.
[c]Female coded as (=1), male (=0).
*$p \leq 0.05$.

by variables gathered at study onset: age, sex, caffeine-/alcohol-intake, smoking method, number of smoked cigarettes, MSF_{sc}, SJL, PSQI, and ESS overall scores. Model assumptions such as the absence of multicollinearity, linearity of independent variables and lack of outliers, were tested beforehand (Stoltzfus, 2011). No model assumptions were violated, and some variables were analyzed separately because many were highly correlated (correlations occurred for MSF_{sc} and SJL, MSF_{sc} and age, SJL and age, PSQI and ESS, sex and number of cigarettes, and age and sex). Only ESS overall scores contributed significantly to the model (i.e. prediction of cessation), with lower scores predicting continuing to smoke. Detailed results can be obtained from Table 3.

Smoking Dosage, Acrophase of Activity, Chronotype, and Social Jetlag

The average cigarette consumption per participant per day was assessed at the beginning of our study. At T0, smoking dosage (cigarettes per day; c/d) was on average across all participants 16 ± 6 c/d (range: 3-37 c/d) without differences between the two groups (quit group: 16 ± 7 c/d; range: 7 37 c/d; continue group: 16 ± 6 c/d; range: 3 28 c/d). After the intervention, even members of the continue group reduced their dosage (10 ± 6 c/d; range: 3-21 c/d). This reduction was significant (Wilcoxon signed-rank test, data not normally distributed: Median (T0) = 14.00, Median (T1) = 9.33, $Z = -3.52$, $N = 21$, $p = \leq 0.001$). Dosage had no association with $\psi_{act\text{-}week}$, MSF_{sc} or SJL during either T0 or T1 (see Spearman's rho in Supplementary Table S2).

MCTQ Database

Cross-sectional data from the MCTQ database (Roenneberg et al., 2019) was used to further investigate the relationship between smoking and SJL (see Figure 6). The relative Social Jetlag of 146,375 valid MCTQ database entries, which had information about smoking habits, was binned in 30-min intervals and the percentage of smokers were calculated for each bin. Both negative and positive SJL was associated with a higher prevalence of smokers: about 25% of those who sleep 2 h earlier on weekends are smokers, which is similar to the late types who sleep 2 h later on weekends than on workday nights as compared to about 12% smokers in those with no differences between workdays and free days.

Comparisons to Population Samples

As a surrogate for a control population, we compared our sample to two age- and sex-matched populations drawn from the MCTQ database (MCTQdb). In the smaller population sample, smokers were not excluded ($n = 4782$) while the larger contained only nonsmokers ($n = 9107$). Although average chronotype

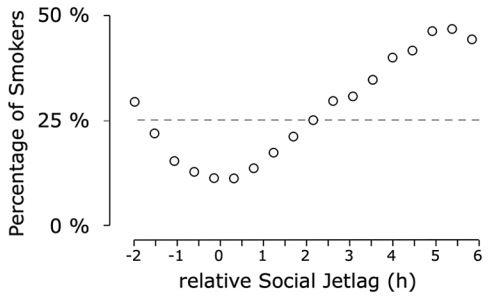


Figure 6. Relative Social Jetlag of the 146,375 valid MCTQ database entries that had information about smoking habits was binned in 30 min intervals and the percentage of smokers were calculated for each bin. Abbreviation: MCTQ = Munich Chronotype Questionnaire.

(MSF_{sc}) was descriptively slightly later and average SJL was descriptively slightly higher in our sample than in the two matched populations, further nonparametric tests showed no significant differences in chronotype or SJL between the samples. This might well be due to the small study sample size.

Albeit not significant, the results reflect increased SJL in the context of smoking because our study sample, consisting of only smokers, showed descriptively increased SJL and later MSF_{sc} than matched population samples. Results are presented in the supplement.

DISCUSSION

A strong correlation between chronotypes or SJL and the probability of being a smoker has previously been shown (Wittmann et al., 2006). However, whether smoking delays circadian phase/chronotype (explanatory scenario-A) or if later chronotype/SJL increases the probability to smoke, is not clear. One could hypothesize that late types suffering from SJL, may more readily smoke as a coping mechanism (explanatory scenario-B). To elucidate the causal directions of these correlations, we examined the two scenarios by accompanying smokers who partook in a cessation program (without nicotine replacements).

The Two Scenarios

Scenario-A predicts a circadian advance with cessation, but our results show no effects of cessation on SJL, chronotype, sleep quality, or daytime sleepiness. Notably, participants showed no significant differences at the start of our intervention that potentially could explain the absence of cessation effects on circadian behavior. In our cohort, the timing of daily behaviors was not different, notably did not advance, between the baseline weeks, and the time after successfully quitting smoking. Our results therefore render scenario-A rather unlikely and further indicate that the circadian measurements were independent from cessation status or number of smoked cigarettes. Changes on the individual level—which were all of small effect sizes (in paired tests)—also contradicted scenario-A: advances, delays, and changes in SJL were largely the same for the two groups. Results from the MCTQ database further corroborate these results, indicating that smoking is fostered by SJL rather than by being a late chronotype: negative SJL (i.e. sleeping earlier on weekends than on workdays) is typical for very early chronotypes, and the prevalence of smokers in those that sleep 2 h earlier on weekends, is similar to that in late types that sleep 2 h later on weekends than on workday nights. Thus, SJL—and not merely being a late type—increased the likelihood of being a smoker.

Furthermore, Wittmann et al. showed that, in their cohort, correlations between SJL and smoking were stronger than correlations between smoking and chronotype (Wittmann et al., 2006). They also argued that the group of over 64-year-old subjects makes a strong case for SJL being responsible regarding smoking: MSF_{sc} in this group was relatively early and narrowly distributed. Smoking and chronotype did not correlate in these subjects. However, when analyzing the elderly subjects who still worked separately, SJL and smoking did correlate, while chronotype and smoking still did not (Wittmann et al., 2006).

SJL has been widely reported to be associated with various aspects of human health, for example, depressive symptoms (Levandovski et al., 2011), lower academic/work performance (McGowan et al., 2020; Yong et al., 2016) and higher cardiovascular or metabolic risks (Koopman et al., 2017; Parsons et al., 2015; Wong et al., 2015). Wittmann et al. suggest that smoking and/or drinking add to the negative effects of SJL (Wittmann et al., 2010). Increased SJL is also associated with higher cortisol levels, indicating an increased activation of the hypothalamic-pituitary-adrenal axis (HPA or commonly known as stress-axis) (Rutters et al., 2014). SJL has further been linked to increased daytime sleepiness (Choi et al., 2019; Komada et al., 2016). A combination of these mentioned effects might contribute to start/maintain smoking.

Our study therefore suggests that reduction of SJL should be part of smoking (and possibly other stimulant) prevention. This is especially pressing considering adolescence, during which the highest SJL is experienced, compared to other age groups (Roenneberg et al., 2007, 2012) and during which most people smoke for the first time (U.S. Department of Health and Human Services, 2014; Wellman et al., 2016).

Smoking Dosage

It could be argued that we did not detect any effects/differences between the groups because smoking dosage significantly decreased in the continue group. Dosage was not associated with MSF_{sc}, SJL or $\psi_{act\text{-}week}$ and these parameters did not change in any group over the course of our intervention. Therefore, we see our results as independent of smoking dosage and argue that they are best understood by way of the dichotomy of being a smoker or not, which has also already been shown by Wittman et al. (2006).

Smoking as a Potential Masking Factor

Nicotine might affect sleeping behavior without changing the phase of the circadian clock. While tobacco use has been shown to alter clock gene expression in lung tissue of rodents (Hwang et al.), we do not know of any work investigating masking of entrainment of the human clock specifically in regard to smoking. It is conceivable that experiencing nicotine addiction might result in earlier wake-up times due to craving (e.g. to smoke the first cigarette of the day (Chandra et al., 2007, 2011; Tiffany and Wray, 2012), and that smoking in the evening might delay bed times because nicotine fosters arousal (Ernst et al., 2001; Myers et al., 2008). This masking phenomenon, might not change the mid-phase of sleep because smokers procrastinate in the evening (due to nicotine arousal effects) and wake up earlier (due to craving), resulting in no great change in mid-sleep. In our study, we aimed to further investigate the known correlation between smoking and SJL. We demonstrate that chronotype or SJL is not different depending on cessation status and therefore argue that smoking is used to cope with SJL and its effects. Whether and in what way smoking may act as a masking factor for circadian rhythms, needs further investigation.

The Role of Sleep Quality

In our sample, continuing to smoke was associated with lower daytime sleepiness (ESS), which evokes two possible explanations: (1) smoking reduces daytime sleepiness (e.g. by fostering arousal (Griesar et al., 2002; Thiel and Fink, 2007; Trimmel and Wittberger, 2004)) and (2) smokers experiencing higher daytime sleepiness might be more motivated to quit. Daytime sleepiness is often associated with low sleep quality and smokers can suffer from low sleep quality (Cohrs et al., 2014; Hu et al., 2007; Jaehne et al., 2012; Phillips and Danner, 1995; Wetter and Young, 1994) and a higher prevalence of lighter sleep stages compared to nonsmokers (Zhang et al., 2006, 2008). However, daytime sleepiness in smokers is a complex issue. Although our ESS-results show that continuing to smoke is associated with lower daytime sleepiness, the opposite has also been reported (Braeckman et al., 2011; Kaur and Singh, 2017; Theorell-Haglöw et al., 2015). Interestingly, daytime sleepiness showed no significant difference between the two outcome groups at study onset, despite being a significant predictor for continuing to smoke, which points to a need for further investigation.

The fact that ESS scores slightly decreased in both groups after the intervention (also in the continue group, which collectively significantly reduced their cigarette consumption), further indicates that daytime sleepiness might have a complex interaction with cessation: it is not only a preintervention predictor for continuing to smoke (as described above) but may be also be a postintervention support for success (positive feedback) in successfully quitting individuals. Continuing smokers, on the contrary, might be relieved (even more) from the pressure to quit, since subjective strain is further reduced (if negative effects of smoking on sleep are in fact dose-dependent, which has been shown (Gillin et al., 1994; Jaehne et al., 2012)).

Sleep quality (PSQI and ESS) in our sample was lower than considered healthy by the questionnaire developers (Buysse et al., 1989; M. W. Johns, 1991). If smoking influences sleep quality, an improvement with cessation should be expected, which we did not find in the limited time we analyzed after cessation (improvements in ESS not significant, PSQI slightly worsened). Besides the explanation that the postintervention period was too short to reveal such improvement in sleep quality, this apparent contradiction could indicate that sleep quality and smoking are associated because bad sleep is a reason for and not a consequence of smoking (similar to SJL, see above). Detrimental effects of cessation on sleep quality have also been described (Colrain et al., 2004; Prosise et al., 1994). Thus, the relationship between smoking and sleep quality/daytime sleepiness needs more research and discussion.

CONCLUSION AND OUTLOOK

Our results support previous findings about the association of SJL and smoking. They advance our understanding of the relationship between the circadian clock and smoking and make recommendations for decreasing nicotine addiction by reducing SJL.

The results of our intervention protocol show that cessation does not affect chronotype (a surrogate for the PoE of the circadian clock) and therefore suggest that smoking is a response to SJL rather than delaying circadian phase, that is, producing later chronotypes and thereby increasing SJL. Further studies are needed to understand the interaction of sleep quality, daytime sleepiness, and smoking, as well as the long-term effects of cessation on the circadian clock and sleep, which should ideally follow subjects over a longer time.

LIMITATIONS

(1) Our sample was relatively small with a female majority. (2) Participants answered the same questions at the beginning and the end of the study, so that an influence of a "known" questionnaire cannot be ruled out. (3) Since the MCTQ refers to the "previous 6 weeks," its answers at study begin do not correspond to the recorded actimetry as they do at study end although MCTQ variables demonstrated a good correspondence to actimetry data during T0. (4) DST changes during our study, might have influenced measurements and results. However, we corrected for the DST changes. Notably both corrected and uncorrected datasets produced the same result in reference to the relevant parameters discussed here. (5) As to be expected in long-range studies, seasons (different photoperiods) may have influenced our results. (6) Actimetry compliance varied in the cohort, so that variable time series lengths were analyzed. (7) As per the a priori power calculation, our study was underpowered to detect differences of small to moderate effect sizes and may have been underpowered to detect differences not related to the main objective (other outcomes). We therefore cannot rule out that our study may have been unable to detect potentially existing small effect sizes due to our small sample size.

ACKNOWLEDGMENTS

The authors would like to thank the participants for their time and cooperation. They also thank Giulia Zerbini for revising an earlier version of the manuscript and her valuable feedback. NG received funding from the FoeFoLe program of the LMU (Registration No. 37/2013). The Psychiatric Clinic at the LMU and its Tobacco Outpatient Clinic supported this study financially. LKP received fellowships from Coordenação de Aperfeiçoamento de Pessoal de Nível Superior—Brasil (CAPES).

AUTHOR CONTRIBUTIONS

TR and NG designed the study. NG and AR collected the data. NG, LKP, and TR analyzed the data. NG, LKP, TR, AR, and TRüther revised the manuscript.

CONFLICT OF INTEREST STATEMENT

TR is founder and CSO of the company Chronsulting UG. The remaining authors declare that there is no conflict of interest.

DATA AVAILABILITY STATEMENT

The underlying research materials related to this study (data set, models) are available on request from the corresponding author (TR).

ORCID IDS

Neda Ghotbi https://orcid.org/0000-0003-3405-4608
Luísa K. Pilz https://orcid.org/0000-0001-7328-6204

NOTE

Supplementary material is available for this article online.

REFERENCES

Abdi H (2007) Bonferroni and Šidák corrections for multiple comparisons. In: Salkind NJ, editor. Encyclopedia of measurement and statistics. Thousand Oaks (CA): Sage. p. 103-107.

Adan A (1994) Chronotype and personality factors in the daily consumption of alcohol and psychostimulants. Addiction 89:455-462.

Antypa N, Vogelzangs N, Meesters Y, Schoevers R, and Penninx BWJH (2016) Chronotype associations with depression and anxiety disorders in a Large Cohort Study. Depress Anxiety 33:75-83.

Braeckman L, Verpraet R, Van Risseghem M, Pevernagie D, and De Bacquer D (2011) Prevalence and correlates of poor sleep quality and daytime sleepiness in Belgian truck drivers. Chronobiol Int 28:126-134.

Broms U, Pennanen M, Patja K, Ollila H, Korhonen T, Kankaanpää A, Haukkala A, Tuulio-Henriksson A, Koskenvuo M, Kronholm E, et al. (2012) Diurnal evening

type is associated with current smoking, nicotine dependence and nicotine intake in the population based national FINRISK 2007 Study. J Addict Res Ther S2:002.

Buysse DJ, Reynolds XF 3rd, Monk TH, Berman SR, and Kupfer DJ (1989) The Pittsburgh Sleep Quality Index: a new instrument for psychiatric practice and research. Psychiatry Res 28:193-213.

Carpenter JS and Andrykowski MA (1998) Psychometric evaluation of the Pittsburgh Sleep Quality Index. J Psychosom Res 45:5-13.

Chandra S, Shiffman S, Scharf DM, Dang Q, and Shadel WG (2007) Daily smoking patterns, their determinants, and implications for quitting. Exp Clin Psychopharmacol 15:67.

Chandra S, Scharf D, and Shiffman S (2011) Within-day temporal patterns of smoking, withdrawal symptoms, and craving. Drug Alcohol Depend 117:118-125.

Choi HJ, Lee YJ, Yoo YJ, Cho YW, and Moon H-J (2019) The effects of chronotype and social jetlag on medical students. Sleep Biol Rhythms 17:269-276.

Cohrs S, Rodenbeck A, Riemann D, Szagun B, Jaehne A, Brinkmeyer J, Gründer G, Wienker T, Diaz-Lacava A, Mobascher A, et al. (2014) Impaired sleep quality and sleep duration in smokers: results from the German Multicenter Study on Nicotine Dependence. Addict Biol 19:486-496.

Colrain IM, Trinder J, and Swan GE (2004) The impact of smoking cessation on objective and subjective markers of sleep: review, synthesis, and recommendations. Nicotine Tob Res 6:913-925.

Deveci SE, Deveci F, Açik Y, and Tevfik Ozan A (2004) The measurement of exhaled carbon monoxide in healthy smokers and non-smokers. Respir Med 98:551-556.

Duffy JF and Wright KP (2005) Entrainment of the human circadian system by light. J Biol Rhythms 20:326-338.

Ernst M, Heishman SJ, Spurgeon L, and London ED (2001) Smoking history and nicotine effects on cognitive performance. Neuropsychopharmacology 25:313-319.

Fabbian F, Zucchi B, De Giorgi A, Tiseo R, Boari B, Salmi R, Cappadona R, Gianesini G, Bassi E, Signani F, et al. (2016) Chronotype, gender and general health. Chronobiol Int 33:863-882.

Faul F, Erdfelder E, Buchner A, and Lang A-G (2009) Statistical power analyses using G* Power 3.1: tests for correlation and regression analyses. Behav Res Methods 41:1149-1160.

Faul F, Erdfelder E, Lang A-G, and Buchner A (2007) G* Power 3: a flexible statistical power analysis program for the social, behavioral, and biomedical sciences. Behav Res Methods 39:175-191.

Gillin JC, Lardon M, Ruiz C, Golshan S, and Salin-Pascual R (1994) Dose-dependent effects of transdermal nicotine on early morning awakening and rapid eye movement sleep time in nonsmoking normal volunteers. J Clin Psychopharmacol 14. https://journals.lww.com/psychopharmacology/Fulltext/1994/08000/Dose_Dependent_Effects_of_Transdermal_Nicotine_on.6.aspx.

Grandner MA, Kripke DF, Yoon I-Y, and Youngstedt SD (2006) Criterion validity of the Pittsburgh Sleep Quality Index: investigation in a non-clinical sample. Sleep Biol Rhythms 4:129-136.

Griesar WS, Zajdel DP, and Oken BS (2002) Nicotine effects on alertness and spatial attention in non-smokers. Nicotine Tob Res 4:185-194.

Hinkle DE, Wiersma W, and Jurs SG (2003) Applied statistics for the behavioral sciences. Boston: Houghton Mifflin College Division.

Horne JA and Ostberg O (1976) A Self-Assessment Questionnaire to determine morningness-eveningness in human circadian rhythms. Int J Chronobiol 4:97-110.

Hu L, Sekine M, Gaina A, and Kagamimori S (2007) Association between sleep quality and smoking in Japanese civil servants. Sleep Biol Rhythms 5:196-203.

Jaehne A, Unbehaun T, Feige B, Lutz UC, Batra A, and Riemann D (2012) How smoking affects sleep: a polysomnographical analysis. Sleep Med 13:1286-1292.

Javors MA, Hatch JP, and Lamb RJ (2005) Cut-off levels for breath carbon monoxide as a marker for cigarette smoking. Addiction 100:159-167.

Johns M and Hocking B (1997) Daytime sleepiness and sleep habits of Australian workers. Sleep 20:844-847.

Johns MW (1991) A new method for measuring daytime sleepiness: the Epworth Sleepiness Scale. Sleep 14: 540-545.

Johns MW (1992) Reliability and factor analysis of the Epworth Sleepiness Scale. Sleep 15:376-381.

Kantermann T, Sung H, and Burgess HJ (2015) Comparing the Morningness-Eveningness Questionnaire and Munich ChronoType Questionnaire to the Dim Light Melatonin Onset. J Biol Rhythms 30:449-453.

Kapusta ND, Pietschnig J, Plener PL, Blüml V, Lesch OM, and Walter H (2010) Does breath carbon monoxide measure nicotine dependence? J Addict Dis 29:493-499.

Kaur G and Singh A (2017) Excessive daytime sleepiness and its pattern among Indian college students. Sleep Med 29:23-28.

Kitamura S, Hida A, Aritake S, Higuchi S, Enomoto M, Kato M, Vetter C, Roenneberg T, and Mishima K (2014) Validity of the Japanese Version of the Munich ChronoType Questionnaire. Chronobiol Int 31:845-850.

Koegelenberg CFN, Noor F, Bateman ED, van Zyl-Smit RN, Bruning A, O'Brien JA, Smith C, Abdool-Gaffar MS, Emanuel S, Esterhuizen TM, et al. (2014) Efficacy of varenicline combined with nicotine replacement therapy vs varenicline alone for smoking cessation: a randomized clinical trial. JAMA 312:155-161.

Komada Y, Breugelmans R, Drake CL, Nakajima S, Tamura N, Tanaka H, Inoue S, and Inoue Y (2016) Social jetlag

affects subjective daytime sleepiness in school-aged children and adolescents: a study using the Japanese Version of the Pediatric Daytime Sleepiness Scale (PDSS-J). Chronobiol Int 33:1311-1319.

Koopman ADM, Rauh SP, van 't Riet E, Groeneveld L, van der Heijden AA, Elders PJ, Dekker JM, Nijpels G, Beulens JW, and Rutters F (2017) The association between social jetlag, the Metabolic Syndrome, and Type 2 diabetes mellitus in the general population: the New Hoorn Study. J Biol Rhythms 32:359-368.

Kröger C and Gradl S (2007) Das Rauchfrei Programm: Ein Manual Zur Tabakentwöhnung. München: IFT Gesundheitsförderung GmbH.

Kufeld C and Bühringer G (2010) Behandlung Der Tabakabhängigkeit. Berlin (Germany): De Gruyter.

Kwon B and Lee G (2022) Association between chronotype, tobacco use or alcohol use, and high-risk drinking by age group: the Seventh Korea National Health and Nutrition Examination Survey (VII: 2016-2017). Sleep Health 8:491-497.

Levandovski R, Dantas G, Fernandes LC, Caumo W, Torres I, Roenneberg T, Loayza Hidalgo MP, and Allebrandt KV (2011) Depression scores associate with chronotype and social jetlag in a rural population. Chronobiol Int 28:771-778.

Liang K-Y and Zeger SL (1986) Longitudinal data analysis using generalized linear models. Biometrika 73:13-22.

McGowan NM, Uzoni A, Faltraco F, Thome J, and Coogan AN (2020) The impact of social jetlag and chronotype on attention, inhibition and decision making in healthy adults. J Sleep Res 29:e12974.

Middleton ET and Morice AH (2000) Breath carbon monoxide as an indication of smoking habit. Chest 117:758-763.

Mollayeva T, Thurairajah P, Burton K, Mollayeva S, Shapiro CM, and Colantonio A (2016) The Pittsburgh Sleep Quality Index as a screening tool for sleep dysfunction in clinical and non-clinical samples: a systematic review and meta-analysis. Sleep Med Rev 25:52-73.

Myers CS, Taylor RC, Moolchan ET, and Heishman SJ (2008) Dose-related enhancement of mood and cognition in smokers administered nicotine nasal spray. Neuropsychopharmacology 33:588-598.

Noble WS (2009) How does multiple testing correction work? Nature Biotechnol 27:1135.

Parsons MJ, Moffitt TE, Gregory AM, Goldman-Mellor S, Nolan PM, Poulton R, and Caspi A (2015) Social jetlag, obesity and metabolic disorder: investigation in a cohort study. Int J Obes 39:842.

Patrick DL, Cheadle A, Thompson DC, Diehr P, Koepsell T, and Kinne S (1994) The validity of self-reported smoking: a review and meta-analysis. Am J Public Health 84:1086-1093.

Phillips BA and Danner FJ (1995) Cigarette smoking and sleep disturbance. Arch Intern Med 155:734-737.

Pilz LK, Keller LK, Lenssen D, and Roenneberg T (2018) Time to rethink sleep quality: PSQI scores reflect sleep quality on workdays. Sleep 41:zsy029.

Prosise GL, Bonnet MH, Berry RB, and Dickel MJ (1994) Effects of abstinence from smoking on sleep and daytime sleepiness. Chest 105:1136-1141.

Rad M, Kakoie S, Brojeni FN, and Pourdamghan N (2010) Effect of long-term smoking on whole-mouth salivary flow rate and oral health. J Dent Res Dent Clin Dent Prospects 4:110.

Roenneberg T, Allebrandt KV, Merrow M, and Vetter C (2012) Social jetlag and obesity. Curr Biol 22:939-943.

Roenneberg T, Kuehnle T, Juda M, Kantermann T, Allebrandt K, Gordijn M, and Merrow M (2007) Epidemiology of the human circadian clock. Sleep Med Rev 11:429-438.

Roenneberg T, Keller LK, Fischer D, Matera JL, Vetter C, and Winnebeck EC (2015) Human activity and rest in situ. Methods Enzymol 552:257-283.

Roenneberg T, Jairaj Kumar C, and Merrow M (2007) The human circadian clock entrains to sun time. Curr Biol 17:R44-R45.

Roenneberg T, Pilz LK, Zerbini G, and Winnebeck EC (2019) Chronotype and social jetlag: a (self-) critical review. Biology 8:54.

Roenneberg T, Wirz-Justice A, and Merrow M (2003) Life between clocks: daily temporal patterns of human chronotypes. J Biol Rhythms 18:80-90.

Rutters F, Lemmens SG, Adam TC, Bremmer MA, Elders PJ, Nijpels G, and Dekker JM (2014) Is social jetlag associated with an adverse endocrine, behavioral, and cardiovascular risk profile? J Biol Rhythms 29:377-383.

Stead LF, Carroll AJ, and Lancaster T (2017) Group behaviour therapy programmes for smoking cessation. Cochrane Database Syst Rev 3:CD001007.

Steyer R, Ferring D, and Schmitt MJ (1992) States and traits in psychological assessment. Eur J Psychol Assess 8:79-98.

Stoltzfus JC (2011) Logistic regression: a brief primer. Acad Emerg Med 18:1099-1104.

Suh S, Yang H-C, Kim N, Yu JH, Choi S, Yun C-H, and Shin C (2017) Chronotype differences in health behaviors and health-related quality of life: a population-based study among aged and older adults. Behav Sleep Med 15:361-376.

Theorell-Haglöw J, Åkerstedt T, Schwarz J, and Lindberg E (2015) Predictors for development of excessive daytime sleepiness in women: a population-based 10-year follow-up. Sleep 38:1995-2003.

Thiel CM and Fink GR (2007) Visual and auditory alertness: modality-specific and supramodal neural mechanisms and their modulation by nicotine. J Neurophysiol 97:2758-2768.

Tiffany ST and Wray JM (2012) The clinical significance of drug craving. Ann N Y Acad Sci 1248:1-17.

Tonstad S, Tønnesen P, Hajek P, Williams KE, Billing CB, Reeves KR, and Varenicline Phase 3 Study Group (2006) Effect of maintenance therapy with varenicline on smoking cessation: a randomized controlled trial. JAMA 296:64-71.

Trimmel M and Wittberger S (2004) Effects of transdermally administered nicotine on aspects of attention, task load, and mood in women and men. Pharmacol Biochem Behav 78:639-645.

US Department of Health and Human Services (2014) The health consequences of smoking—50 years of progress: a report of the Surgeon General. Atlanta (GA): US Department of Health and Human Services, Centers for Disease Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health.

Wellman RJ, Dugas EN, Dutczak H, O'Loughlin EK, Datta GD, Lauzon B, and O'Loughlin J (2016) Predictors of the onset of cigarette smoking: a systematic review of longitudinal population-based studies in youth. American Journal of Preventive Medicine 51:767-778.

West R, Hajek P, Stead L, and Stapleton J (2005) Outcome criteria in smoking cessation trials: proposal for a common standard. Addiction 100:299-303.

Wetter DW and Young TB (1994) The relation between cigarette smoking and sleep disturbance. Prev Med 23:328-334.

Wickham H, Chang W, and Wickham MH (2016) Package "Ggplot2." Create elegant data visualisations using the grammar of graphics. Version 2. R Foundation for Statistical Computing: Vienna, Austria.

Wittmann M, Dinich J, Merrow M, and Roenneberg T (2006) Social jetlag: misalignment of biological and social time. Chronobiol Int 23:497-509.

Wittmann M, Paulus M, and Roenneberg T (2010) Decreased psychological well-being in late "chronotypes" is mediated by smoking and alcohol consumption. Subst Use Misuse 45:15-30.

Wong PM, Hasler BP, Kamarck TW, Muldoon MF, and Manuck SB (2015) Social jetlag, chronotype, and cardiometabolic risk. J Clin Endocrinol Metab 100:4612-4620.

World Health Organization (2019) WHO global report on trends in prevalence of tobacco use 2000-2025. Geneva (Switzerland): World Health Organization.

Wright KP, McHill AW, Birks BR, Griffin BR, Rusterholz T, and Chinoy ED (2013) Entrainment of the human circadian clock to the natural light-dark cycle. Curr Biol 23:1554-1558.

Yong M, Fischer D, Germann C, Lang S, Vetter C, and Oberlinner C (2016) Are chronotype, social jetlag and sleep duration associated with health measured by work ability index? Chronobiol Int 33:721-729.

Zhang L, Samet J, Caffo B, Bankman I, and Punjabi NM (2008) Power spectral analysis of EEG activity during sleep in cigarette smokers. Chest 133:427-432.

Zhang L, Samet J, Caffo B, and Punjabi NM (2006) Cigarette smoking and nocturnal sleep architecture. Am J Epidemiol 164:529-537.

7. Literaturverzeichnis

1. Antypa, N., Vogelzangs, N., Meesters, Y., Schoevers, R., Penninx, B.W.J.H., 2016. CHRONOTYPE ASSOCIATIONS WITH DEPRESSION AND ANXIETY DISORDERS IN A LARGE COHORT STUDY. Depression & Anxiety (1091-4269) 33, 75–83.

2. Arendt, J., 2006. Melatonin and human rhythms. Chronobiol. Int. 23, 21–37. https://doi.org/10.1080/07420520500464361

3. Arendt, J., Skene, D.J., 2005. Melatonin as a chronobiotic. Sleep medicine reviews 9, 25–39.

4. Baker, T.B., Brandon, T.H., Chassin, L., 2004. Motivational influences on cigarette smoking. Annu. Rev. Psychol. 55, 463–491.

5. Baron, K.G., Reid, K.J., 2014. Circadian misalignment and health. Int Rev Psychiatry 26, 139–154. https://doi.org/10.3109/09540261.2014.911149

6. Beauvalet, J.C., Quiles, C.L., Oliveira, M.A.B. de, Ilgenfritz, C.A.V., Hidalgo, M.P.L., Tonon, A.C., 2017. Social jetlag in health and behavioral research: a systematic review. ChronoPhysiology and Therapy. London. Vol. 7 (2017), p. 19–31.

7. Benloucif, S., Burgess, H.J., Klerman, E.B., Lewy, A.J., Middleton, B., Murphy, P.J., Parry, B.L., Revell, V.L., 2008. Measuring melatonin in humans. Journal of Clinical Sleep Medicine 4, 66–69.

8. Borisenkov, M., Polugrudov, A., Paderin, N., Bakutova, L., 2019. Young inhabitants of the North with late chronotype and social jetlag consume more high-calorie foods and alcohol. Biological Rhythm Research 50, 418–428.

9. Brandon, T.H., Juliano, L.M., Copeland, A.L., 1999. Expectancies for tobacco smoking.

10. Braun, R., Kath, W.L., Iwanaszko, M., Kula-Eversole, E., Abbott, S.M., Reid, K.J., Zee, P.C., Allada, R., 2018. Universal method for robust detection of circadian state from gene expression. Proc Natl Acad Sci USA 115, E9247. https://doi.org/10.1073/pnas.1800314115

11. Broms, U., Pennanen, M., Patja, K., Ollila, H., Korhonen, T., Kankaanpää, A., Haukkala, A., Tuulio-Henriksson, A., Koskenvuo, M., Kronholm, E., 2012. Diurnal evening type is associated with current smoking, nicotine dependence and nicotine intake in the population based National FINRISK 2007 Study. Journal of addiction research & therapy.

12. Choi, H.J., Lee, Y.J., Yoo, Y.J., Cho, Y.W., Moon, H.-J., 2019. The effects of chronotype and social jetlag on medical students. Sleep and Biological Rhythms 17, 269–276.

13. Copeland, A.L., Brandon, T.H., Quinn, E.P., 1995. The Smoking Consequences Questionnaire-Adult: Measurement of smoking outcome expectancies of experienced smokers. Psychological Assessment 7, 484.

14. De Almeida, E.A., Di Mascio, P., Harumi, T., Warren Spence, D., Moscovitch, A., Hardeland, R., Cardinali, D.P., Brown, G.M., Pandi-Perumal, S.R., 2011. Measurement of melatonin in body fluids: standards, protocols and procedures. Child's Nervous System 27, 879–891.

15. DHHS, U., 2014. The Health Consequences of Smoking—50 Years of Progress: A Report of the Surgeon General. Atlanta, GA: US Department of Health and Human Services, Centers for Disease Control and Prevention, National Center for

Chronic Disease Prevention and Health Promotion, Office on Smoking and Health 17.

16. Duffy, J.F., Wright, K.P., 2005. Entrainment of the Human Circadian System by Light. J Biol Rhythms 20, 326–338. https://doi.org/10.1177/0748730405277983

17. Ernst, M., Heishman, S.J., Spurgeon, L., London, E.D., 2001. Smoking history and nicotine effects on cognitive performance. Neuropsychopharmacology 25, 313–319.

18. Fidler, J.A., West, R., 2009. Self-perceived smoking motives and their correlates in a general population sample. Nicotine & Tobacco Research 11, 1182–1188.

19. Ghotbi, N., Pilz, L.K., Winnebeck, E.C., Vetter, C., Zerbini, G., Lenssen, D., Frighetto, G., Salamanca, M., Costa, R., Montagnese, S., Roenneberg, T., 2020. The μMCTQ: An Ultra-Short Version of the Munich ChronoType Questionnaire. Journal of Biological Rhythms 35, 98–110. https://doi.org/10.1177/0748730419886986

20. Ghotbi, N., Rabenstein, A., Pilz, L.K., Rüther, T., Roenneberg, T., 2023. Chronotype, Social Jetlag, and Nicotine Use. J Biol Rhythms 38, 392–406. https://doi.org/10.1177/07487304231177197

21. Gradisar, M., Kahn, M., Micic, G., Short, M., Reynolds, C., Orchard, F., Bauducco, S., Bartel, K., Richardson, C., 2022. Sleep's role in the development and resolution of adolescent depression. Nature Reviews Psychology 1, 512–523.

22. Haynie, D.L., Lewin, D., Luk, J.W., Lipsky, L.M., O'Brien, F., Iannotti, R.J., Liu, D., Simons-Morton, B.G., 2018. Beyond sleep duration: Bidirectional associations among chronotype, social jetlag, and drinking behaviors in a longitudinal sample of US high school students. Sleep 41, zsx202.

23. Heishman, S.J., Kleykamp, B.A., Singleton, E.G., 2010. Meta-analysis of the acute effects of nicotine and smoking on human performance. Psychopharmacology 210, 453–469.

24. Horne, J.A., Ostberg, O., 1976. A self-assessment questionnaire to determine morningness-eveningness in human circadian rhythms. Int J Chronobiol 4, 97–110.

25. Hu, L., Sekine, M., Gaina, A., Kagamimori, S., 2007. Association between sleep quality and smoking in Japanese civil servants. Sleep and Biological Rhythms 5, 196–203.

26. Jaehne, A., Unbehaun, T., Feige, B., Lutz, U.C., Batra, A., Riemann, D., 2012. How smoking affects sleep: A polysomnographical analysis. Sleep Medicine 13, 1286–1292. https://doi.org/10.1016/j.sleep.2012.06.026

27. Kantermann, T., Sung, H., Burgess, H.J., 2015. Comparing the Morningness-Eveningness Questionnaire and Munich ChronoType Questionnaire to the Dim Light Melatonin Onset. J. Biol. Rhythms 30, 449–453. https://doi.org/10.1177/0748730415597520

28. Kassel, J.D., Stroud, L.R., Paronis, C.A., 2003. Smoking, stress, and negative affect: correlation, causation, and context across stages of smoking. Psychological bulletin 129, 270.

29. Kitamura, S., Hida, A., Aritake, S., Higuchi, S., Enomoto, M., Kato, M., Vetter, C., Roenneberg, T., Mishima, K., 2014. Validity of the Japanese version of the Munich ChronoType Questionnaire. Chronobiol. Int. 31, 845–850. https://doi.org/10.3109/07420528.2014.914035

30. Klerman, E.B., Brager, A., Carskadon, M.A., Depner, C.M., Foster, R., Goel, N., Harrington, M., Holloway, P.M., Knauert, M.P., LeBourgeois, M.K., 2022. Keeping an eye on circadian time in clinical research and medicine. Clinical and Translational Medicine 12, e1131.

31. Klerman, E.B., Gershengorn, H.B., Duffy, J.F., Kronauer, R.E., 2002. Comparisons of the variability of three markers of the human circadian pacemaker. Journal of biological rhythms 17, 181–193.

32. Knutson, K.L., von Schantz, M., 2018. Associations between chronotype, morbidity and mortality in the UK Biobank cohort. Chronobiology International 35, 1045–1053. https://doi.org/10.1080/07420528.2018.1454458

33. Ko, C.H., Takahashi, J.S., 2006. Molecular components of the mammalian circadian clock. Human Molecular Genetics 15, R271–R277. https://doi.org/10.1093/hmg/ddl207

34. Kobus, K., 2003. Peers and adolescent smoking. Addiction 98, 37–55.

35. Komada, Y., Breugelmans, R., Drake, C.L., Nakajima, S., Tamura, N., Tanaka, H., Inoue, S., Inoue, Y., 2016. Social jetlag affects subjective daytime sleepiness in school-aged children and adolescents: A study using the Japanese version of the Pediatric Daytime Sleepiness Scale (PDSS-J). Chronobiology international 33, 1311–1319.

36. Koopman, A.D., Rauh, S.P., van 't Riet, E., Groeneveld, L., Van Der Heijden, A.A., Elders, P.J., Dekker, J.M., Nijpels, G., Beulens, J.W., Rutters, F., 2017. The association between social jetlag, the metabolic syndrome, and type 2 diabetes mellitus in the general population: the new Hoorn study. Journal of biological rhythms 32, 359–368.

37. Levandovski, R., Dantas, G., Fernandes, L.C., Caumo, W., Torres, I., Roenneberg, T., Hidalgo, M.P.L., Allebrandt, K.V., 2011. Depression scores associate with chronotype and social jetlag in a rural population. Chronobiology international 28, 771–778.

38. Lewy, A.J., Sack, R.L., 1989. The dim light melatonin onset as a marker for circadian phase position. Chronobiol. Int. 6, 93–102.

39. Logan, R.W., Hasler, B.P., Forbes, E.E., Franzen, P.L., Torregrossa, M.M., Huang, Y.H., Buysse, D.J., Clark, D.B., McClung, C.A., 2018. Impact of sleep and circadian rhythms on addiction vulnerability in adolescents. Biological psychiatry 83, 987–996.

40. Loock, A.-S., Khan Sullivan, A., Reis, C., Paiva, T., Ghotbi, N., Pilz, L.K., Biller, A.M., Molenda, C., Vuori-Brodowski, M.T., Roenneberg, T., Winnebeck, E.C., 2021. Validation of the Munich Actimetry Sleep Detection Algorithm for estimating sleep–wake patterns from activity recordings. Journal of Sleep Research 30, e13371. https://doi.org/10.1111/jsr.13371

41. Lujic, C., Reuter, M., Netter, P., 2005. Psychobiological theories of smoking and smoking motivation. European psychologist 10, 1–24.

42. McEwen, B.S., Karatsoreos, I.N., 2015. Sleep Deprivation and Circadian Disruption: Stress, Allostasis, and Allostatic Load. Sleep medicine clinics 10, 1.

43. McGowan, N.M., Uzoni, A., Faltraco, F., Thome, J., Coogan, A.N., 2020. The impact of social jetlag and chronotype on attention, inhibition and decision making in healthy adults. Journal of sleep research 29, e12974.

44. Okajima, I., Komada, Y., Ito, W., Inoue, Y., 2021. Sleep Debt and Social Jetlag Associated with Sleepiness, Mood, and Work Performance among Workers in Japan. International Journal of Environmental Research and Public Health 18. https://doi.org/10.3390/ijerph18062908

45. Parrott, A.C., 1995. Stress modulation over the day in cigarette smokers. Addiction 90, 233–244.

46. Parrott, A.C., 1994. Individual differences in stress and arousal during cigarette smoking. Psychopharmacology 115, 389–396.

47. Parsons, M.J., Moffitt, T.E., Gregory, A., Goldman-Mellor, S., Nolan, P., Poulton, R., Caspi, A., 2015. Social jetlag, obesity and metabolic disorder: investigation in a cohort study. International Journal of Obesity 39, 842.

48. Phillips, B.A., Danner, F.J., 1995. Cigarette Smoking and Sleep Disturbance. Archives of Internal Medicine 155, 734–737. https://doi.org/10.1001/archinte.1995.00430070088011

49. Pilz, L.K., Keller, L.K., Lenssen, D., Roenneberg, T., 2018. Time to rethink sleep quality: PSQI scores reflect sleep quality on workdays. Sleep. https://doi.org/10.1093/sleep/zsy029

50. Porcheret, K., Wald, L., Fritschi, L., Gerkema, M., Gordijn, M., Merrrow, M., Rajaratnam, S.M., Rock, D., Sletten, T.L., Warman, G., 2018. Chronotype and environmental light exposure in a student population. Chronobiology international 35, 1365–1374.

51. Roenneberg, T., 2012. What is chronotype? Sleep and Biological Rhythms 10, 75–76. https://doi.org/10.1111/j.1479-8425.2012.00541.x

52. Roenneberg, T., Allebrandt, K.V., Merrow, M., Vetter, C., 2012. Social jetlag and obesity. Curr. Biol. 22, 939–943. https://doi.org/10.1016/j.cub.2012.03.038

53. Roenneberg, T., Daan, S., Merrow, M., 2003a. The art of entrainment. J. Biol. Rhythms 18, 183–194. https://doi.org/10.1177/0748730403018003001

54. Roenneberg, T., Foster, R.G., Klerman, E.B., 2022. The circadian system, sleep, and the health/disease balance: a conceptual review. Journal of Sleep Research e13621.

55. Roenneberg, T., Keller, L.K., Fischer, D., Matera, J.L., Vetter, C., Winnebeck, E.C., 2015. Human activity and rest in situ. Meth. Enzymol. 552, 257–283. https://doi.org/10.1016/bs.mie.2014.11.028

56. Roenneberg, T., Kuehnle, T., Juda, M., Kantermann, T., Allebrandt, K., Gordijn, M., Merrow, M., 2007a. Epidemiology of the human circadian clock. Sleep Med Rev 11, 429–438. https://doi.org/10.1016/j.smrv.2007.07.005

57. Roenneberg, T., Kumar, C.J., Merrow, M., 2007b. The human circadian clock entrains to sun time. Curr. Biol. 17, R44-45. https://doi.org/10.1016/j.cub.2006.12.011

58. Roenneberg, T., Pilz, L.K., Zerbini, G., Winnebeck, E.C., 2019. Chronotype and social jetlag: a (self-) critical review. Biology 8, 54.

59. Roenneberg, T., Wirz-Justice, A., Merrow, M., 2003b. Life between clocks: daily temporal patterns of human chronotypes. J. Biol. Rhythms 18, 80–90.

60. Rutters, F., Lemmens, S.G., Adam, T.C., Bremmer, M.A., Elders, P.J., Nijpels, G., Dekker, J.M., 2014. Is social jetlag associated with an adverse endocrine, behavioral, and cardiovascular risk profile? Journal of biological rhythms 29, 377–383.

61. Samet, J.M., 2013. Tobacco smoking: the leading cause of preventable disease worldwide. Thoracic surgery clinics 23, 103–112.

62. Smith, R.F., McDonald, C.G., Bergstrom, H.C., Ehlinger, D.G., Brielmaier, J.M., 2015. Adolescent nicotine induces persisting changes in development of neural connectivity. Neuroscience & Biobehavioral Reviews 55, 432–443.

63. Steyer, R., Ferring, D., Schmitt, M.J., 1992. States and traits in psychological assessment. European Journal of Psychological Assessment.

64. Stothard, E.R., McHill, A.W., Depner, C.M., Birks, B.R., Moehlman, T.M., Ritchie, H.K., Guzzetti, J.R., Chinoy, E.D., LeBourgeois, M.K., Axelsson, J., Wright, K.P., 2017. Circadian Entrainment to the Natural Light-Dark Cycle across Seasons and the Weekend. Current Biology 27, 508–513. https://doi.org/10.1016/j.cub.2016.12.041

65. Tamura, N., Komada, Y., Inoue, Y., Tanaka, H., 2022. Social jetlag among Japanese adolescents: Association with irritable mood, daytime sleepiness, fatigue, and poor academic performance. Chronobiology International 39, 311–322. https://doi.org/10.1080/07420528.2021.1996388

66. Tarokh, L., Short, M., Crowley, S.J., Fontanellaz-Castiglione, C.E.G., Carskadon, M.A., 2019. Sleep and Circadian Rhythms in Adolescence. Current Sleep Medicine Reports 5, 181–192. https://doi.org/10.1007/s40675-019-00155-w

67. Trauth, J.A., Seidler, F.J., Ali, S.F., Slotkin, T.A., 2001. Adolescent nicotine exposure produces immediate and long-term changes in CNS noradrenergic and dopaminergic function. Brain Research 892, 269–280.

68. Wellman, R.J., Dugas, E.N., Dutczak, H., O'Loughlin, E.K., Datta, G.D., Lauzon, B., O'Loughlin, J., 2016. Predictors of the Onset of Cigarette Smoking: A Systematic Review of Longitudinal Population-Based Studies in Youth. American Journal of Preventive Medicine 51, 767–778. https://doi.org/10.1016/j.amepre.2016.04.003

69. West, R., 1993. Beneficial effects of nicotine: fact or fiction? Addiction.

70. West, R., Hajek, P., Stead, L., Stapleton, J., 2005. Outcome criteria in smoking cessation trials: proposal for a common standard. Addiction 100, 299–303. https://doi.org/10.1111/j.1360-0443.2004.00995.x

71. Wetter, D.W., Smith, S.S., Kenford, S.L., Jorenby, D.E., Fiore, M.C., Hurt, R.D., Offord, K.P., Baker, T.B., 1994. Smoking outcome expectancies: factor structure, predictive validity, and discriminant validity. Journal of abnormal psychology 103, 801.

72. Wetter, D.W., Young, T.B., 1994. The Relation Between Cigarette Smoking and Sleep Disturbance. Preventive Medicine 23, 328–334. https://doi.org/10.1006/pmed.1994.1046

73. Wittenbrink, N., Ananthasubramaniam, B., Münch, M., Koller, B., Maier, B., Weschke, C., Bes, F., de Zeeuw, J., Nowozin, C., Wahnschaffe, A., Wisniewski, S., Zaleska, M., Bartok, O., Ashwal-Fluss, R., Lammert, H., Herzel, H., Hummel, M., Kadener, S., Kunz, D., Kramer, A., 2018. High-accuracy determination of internal circadian time from a single blood sample. J Clin Invest 128, 3826–3839. https://doi.org/10.1172/JCI120874

74. Wittmann, M., Dinich, J., Merrow, M., Roenneberg, T., 2006. Social jetlag: misalignment of biological and social time. Chronobiology international 23, 497–509.

75. Wittmann, M., Paulus, M., Roenneberg, T., 2010. Decreased Psychological Well-Being in Late 'Chronotypes' Is Mediated by Smoking and Alcohol Consumption. Substance Use & Misuse 45, 15–30. https://doi.org/10.3109/10826080903498952

76. Wong, P.M., Hasler, B.P., Kamarck, T.W., Muldoon, M.F., Manuck, S.B., 2015. Social Jetlag, Chronotype, and Cardiometabolic Risk. J. Clin. Endocrinol. Metab. 100, 4612–4620. https://doi.org/10.1210/jc.2015-2923

77. World Health Organization, 2019. WHO global report on trends in prevalence of tobacco use 2000-2025. World Health Organization.

78. Wright, K.P., McHill, A.W., Birks, B.R., Griffin, B.R., Rusterholz, T., Chinoy, E.D., 2013. Entrainment of the Human Circadian Clock to the Natural Light-Dark Cycle. Current Biology 23, 1554–1558. https://doi.org/10.1016/j.cub.2013.06.039

79. Yong, M., Fischer, D., Germann, C., Lang, S., Vetter, C., Oberlinner, C., 2016. Are chronotype, social jetlag and sleep duration associated with health measured by Work Ability Index? Chronobiology international 33, 721–729.

80. Yuan, M., Cross, S.J., Loughlin, S.E., Leslie, F.M., 2015. Nicotine and the adolescent brain. The Journal of physiology 593, 3397–3412.

Danksagung

Mein besonderer Dank gilt Till. Zunächst für die Möglichkeit an diesen interessanten Projekten zu arbeiten, bei denen ich sehr viel lernen durfte und viel Spaß hatte. Auch für seine so bereichernde Begleitung, wissenschaftlich wie zwischenmenschlich, möchte ich ihm danken. Seine stete Fürsorge und Kreativität, das entgegengebrachte Vertrauen und unsere vielen guten Gespräche, sind von großem persönlichem Wert für mich.

Ich danke meinen Kolleg:innen im IMP für die schöne Zeit. Unsere Zusammenarbeit und unsere spannenden Diskussionen bereiteten mir viel Freude. Insbesondere Luísa möchte ich für die wunderbaren Kooperationen, ihr stets offenes Ohr und ihre klugen Ratschläge von Herzen danken.

Den Teilnehmenden der Studien, sowie allen Mitwirkenden und Kooperationspartner:innen, die hier nicht im Einzelnen genannt werden, möchte ich herzlichen Dank aussprechen, da diese Arbeiten ohne sie nicht möglich gewesen wären.

Dem FoeFoLe-Stipendienprogramm danke ich für die finanzielle und wissenschaftliche Förderung.

Ich danke meiner Familie und insbesondere meinen Eltern für ihre Zuversicht und ihre liebevolle, immer verlässliche Unterstützung. Sie inspirieren mich durch ihr Wohlwollen und ihrem Geschenk an mich zu glauben. Elias, Abtin und meinen Freund:innen danke ich dafür, dass sie sich innerhalb dieser Promotion mit mir gefreut und mitgefiebert haben – beinahe so als wäre es ihre eigene. Ich bin sehr froh darüber, dass es Euch gibt!