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Verzeichnis der Publikationen zur kumulativen Habilitation

1. Marzell R, Kupfer J, Reichwein G, Gieler U, **Schut C*.** Itch induction by audiovisual stimuli and histamine iontophoresis: a randomized, controlled non-inferiority study. *British Journal of Dermatology* 2020;182:1253-1261 (IF 2022: 11.113)

2. **Schut C^{+*},** Mochizuki H^{+}, Grossman SK, Lin AC, Conklin CJ, Mohamed FB, Gieler U, Kupfer J, Yosipovitch G. Brain processing of contagious itch in patients with atopic dermatitis. *Frontiers in Psychology* 2017 Jul 25;8:1267. doi: 10.3389/fpsyg.2017.01267 (IF 2022: 4.232)

3. **Schut C^{+*},** Bosbach S^{+}, Gieler U, Kupfer J. Personality traits, depression and itch in patients with atopic dermatitis in an experimental setting: a regression analysis. *Acta Dermato Venereologica* 2014;94:20-25 (IF 2022: 3.875)

4. **Schut C^{+*},** Reinisch K^{+}, Classen A, Andres S, Gieler U, Kupfer J. Agreeableness as Predictor of Induced Scratching in Patients with Atopic Dermatitis: A Replication Study. *Acta Dermato Venereologica* 2018;98;32-37 (IF 2022: 3.875)

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6. **Schut C*,** Rädel A, Frey L, Gieler U, Kupfer J. Role of personality and expectations for itch and scratching induced by audiovisual stimuli. *European Journal of Pain* 2016; 20:14-18 (IF 2022: 3.651)

7. **Schut C*,** Grossman S, Gieler U, Kupfer J, Yosipovitch G. Contagious itch: What we know and what we would like to know. *Frontiers in Human Neuroscience* 2015 Feb 11;9:57. doi: 10.3389/fnhum.2015.00057 (IF 2022: 3.473)

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Inhalt

1. Einleitung

Pruritus ist eine Körperempfindung, mit der Menschen immer wieder während ihres Lebens konfrontiert werden (Weisshaar et al., 2003). Bei Patienten mit chronischen Hautkrankheiten ist Pruritus oft so intensiv und lang andauernd, dass er als quälend und sehr belastend empfunden wird (Bilac et al., 2009; Dawn et al., 2009; Globe et al., 2009; Ständer, 2019). Trotz der hohen Prävalenz dieses Symptoms von über 50% bei Patienten mit Hauterkrankungen (Schut et al., 2019) und zumeist bedeutsamen Effekten auf das Verhalten der Betroffenen (Yosipovitch et al., 2003) wurde Pruritus lange Zeit nachrangig behandelt und sogar als nicht weiter untersuchungswürdig angesehen (Weisshaar et al., 2003). Erst in den letzten 20 Jahren wird dem Thema Pruritus vermehrt Aufmerksamkeit geschenkt. 2005 wurde das International Forum for the Study of Itch (IFSI) gegründet. Wissenschaftlerinnen und Wissenschaftler unterschiedlicher Fachrichtungen untersuchen nun vermehrt biopsychosoziale Faktoren, die mit Pruritus bei hautgesunden Probanden und/ oder Patienten mit chronischem Pruritus assoziiert sind oder ihn beeinflussen.

Um Zusammenhänge zwischen unterschiedlichen biopsychosozialen Faktoren und Pruritus experimentell untersuchen zu können, ist es notwendig, Pruritus im Labor zu induzieren. Hierfür stehen verschiedene Methoden der Pruritusinduktion zur Verfügung. Die in den letzten Jahren häufig genutzte Histamin-Iontophorese und Cowhage-Applikation benötigen Pruritogene und machen eine direkte Hautmanipulation unabdingbar. Anders ist dies bei pruritogen-freien Methoden der Pruritusinduktion. Bei ihrer Verwendung macht man sich zunutze, dass auch die Präsentation (audio-)visueller, mit Pruritus assoziierter Stimuli (z.B. Bilder/ Videos von krabbelnden Insekten oder sich kratzenden Personen) eine Veränderung im Pruritus und Kratzverhalten bewirkt. Vorteil dieser Methode ist neben der Nicht-Invasivität eine große Ähnlichkeit zu dem, was Patienten mit chronischen, juckenden Hauterkrankungen in alltäglichen Situationen erleben: Pruritus und Kratzverhalten werden durch die Konfrontation mit audio-visuellen Pruritusstimuli getriggert, so dass der sogenannte Juckreiz-Kratzzirkel angestoßen wird.

Die vorliegenden Studien beleuchten den mit (audio-)visuellen Stimuli erzeugten Pruritus genauer: Die Validierung der Methode der (audio)-visuellen Pruritusinduktion

bildet das methodische Fundament der weiteren Studien (Marzell et al., 2020; Schut et al., 2017), die den Kern dieser medizinpsychologischen Forschungsarbeiten darstellen. Diese widmen sich zum einen der Frage, ob Persönlichkeitsfaktoren, Selbstaufmerksamkeit, Angst und Depression Prädiktoren für pruritogen-frei induzierten Pruritus/ pruritogen-frei induziertes Kratzverhalten (Schut et al., 2014; Schut et al., 2018; Schut et al., 2015b) sind. Zum anderen wird geprüft, ob eine veränderte Informationsgabe zu den anschließend dargebotenen audio-visuellen Pruritusstimuli Unterschiede in der induzierten Pruritusintensität respektive dem induzierten Kratzverhalten bedingt (Schut et al., 2016).

Bevor im Folgenden genauer auf die Zielsetzung dieser Studien eingegangen wird, fasst das aktuelle Kapitel wichtige theoretische und empirische Grundlagen zusammen. Es liefert zunächst einen allgemeinen Überblick über das Thema Pruritus und geht hierbei speziell auf die Definition von Pruritus und Möglichkeiten der Klassifikation, die Epidemiologie und die neuronalen Grundlagen von Pruritus ein. Dass Pruritus mit unterschiedlichen biopsychosozialen Faktoren assoziiert ist, wird anschließend herausgearbeitet. Weiterhin werden pruritogen-gebundene und pruritogen-freie Methoden zur Pruritusinduktion im Labor einander gegenübergestellt sowie ihre Vor- und Nachteile diskutiert. Dabei werden jeweils am Ende eines Unterkapitels sowie abschließend basierend auf den theoretischen Grundlagen offene Fragen zusammengefasst. So wird auf die Ziele der Forschungsarbeiten hingeleitet.

1.1 Definition und Klassifikation von Pruritus

Laut dem deutschen Dermatologen Samuel Hafenreffer handelt es sich bei Pruritus (im Deutschen „Jucken“) um eine „unangenehme Sinnesempfindung, die den Wunsch des Kratzens hervorruft“ (Hafenreffer, 1660). Diese sehr alte Definition wird heute noch verwendet (z.B. Bautista et al., 2014; Darsow et al., 2000; Meng & Steinhoff, 2016), auch wenn sie aufgrund ihrer Einfachheit kritisiert wurde (Savin, 1998). Wichtig ist, dass – auch, wenn per Definition Pruritus den Wunsch des Kratzens zur Folge hat – Pruritus und Kratzverhalten nur gering positiv miteinander korrelieren (Holle et al., 2012; Schut et al., 2015b). Die Sinnesempfindung Pruritus mündet also nicht immer und nicht bei allen Betroffenen in einer Veränderung des Verhaltens. Allein diese Tatsache macht es plausibel, personenbezogene Faktoren zu betrachten, die bei

Vorhandensein von Pruritus eine Veränderung des Kratzverhaltens moderieren (Verhoeven et al., 2008).

Bezugnehmend auf die *Dauer* des Pruritus unterscheidet man akuten von chronischem Pruritus, wobei akuter Pruritus per Definition eine Dauer von sechs Wochen nicht überschreitet und chronischer Pruritus immer dann vorliegt, wenn er länger als sechs Wochen anhält (Ständer et al., 2007). Es wird diskutiert, ob chronischer Pruritus nicht nur als Symptom von Krankheiten angesehen werden sollte, sondern auch eine eigenständige Erkrankung darstellen kann (Ständer, 2019).

Hinsichtlich des *Ortes des Auftretens* gibt es per Definition des IFSI drei Kategorien von Pruritus: Pruritus auf kranker Haut (Gruppe I), Pruritus auf nicht-kranker, nicht entzündeter Haut (Gruppe II) und Pruritus aufgrund chronischer, sekundärer Kratzläsionen (Gruppe III). Die *Ursache für Pruritus* der Gruppe I ist dermatologischer Art. Pruritus der Gruppe II kann systemisch, neurologisch oder psychogen verursacht sein, wohingegen Pruritus der Gruppe III einen dermatologischen, systemischen, neurologischen oder psychogenen Ursprung haben kann. Darüber hinaus gibt es Situationen, in denen keine klare Zuordnung für Pruritus vorgenommen werden kann (Ständer et al., 2007).

1.2 Epidemiologie

Studien zur Epidemiologie von Pruritus sind rar (Weisshaar & Dalgard, 2009; Weisshaar et al., 2019) und stammen zumeist aus Europa (Leader et al., 2015). Eine bevölkerungsbezogene Studie aus Skandinavien, in der weder zwischen Patienten mit Hauterkrankungen und hautgesunden Probanden noch zwischen akutem und chronischem Pruritus unterschieden wurde, zeigte eine Punktprävalenz für Pruritus von 8,4% bei Erwachsenen (Dalgard et al., 2004). In Studien, die in Deutschland durchgeführt wurden, lag die Punktprävalenz für chronischen Pruritus in der erwachsenen Allgemeinbevölkerung zwischen 13,5% und 15,4% (Matterne et al., 2009; Matterne et al., 2011; Matterne et al., 2013) und bei 16,8%, wenn lediglich die arbeitende Bevölkerung betrachtet wurde (Schut et al., 2019; Ständer et al., 2010).

Bei Studien, in denen die Prävalenz von Pruritus bei Patienten mit Hauterkrankungen bestimmt wurde, handelt es sich oft um Untersuchungen, die in einzelnen Zentren

durchgeführt wurden (Kopyciok et al., 2016; Mollanazar et al., 2015; Sarikaya Solak et al., 2016), nur Patienten mit einer bestimmten Hauterkrankung einschlossen (Yosipovitch et al., 2002) und/ oder in denen keine Kontrollgruppe hautgesunder Probanden (Verhoeven et al., 2007) hinsichtlich des Auftretens von Pruritus befragt wurde (siehe auch Schut et al., 2019). Deswegen wurde vor wenigen Jahren eine europäische Multicenter-Studie durchgeführt, in die sowohl hautgesunde Probanden als auch Patienten mit Hauterkrankungen aus 13 unterschiedlichen Ländern eingeschlossen wurden (Schut et al., 2019). Von den 3530 befragten Patienten mit Hauterkrankungen berichteten in dieser Studie 54,3%, aktuell Pruritus zu haben, während 8% der 1094 hautgesunden Kontrollprobanden Pruritus zum Zeitpunkt der Befragung angaben. Die Prävalenz von chronischem Pruritus betrug in der Gruppe der Patienten mit Hauterkrankungen 37%, während 5% der Hautgesunden angaben, Pruritus zu haben, der länger als sechs Wochen andauert. Die Patientengruppen mit den höchsten Punktprävalenzraten für akuten Pruritus waren Patienten mit unklassifiziertem Pruritus, Prurigo, Neurodermitis (ND) und Handekzem (alle Prävalenzen > 82,3%).

1.3 Neuronale Grundlage von Pruritus

Pruritus geht per Definition – wie bereits erläutert – mit dem Wunsch des Kratzens einher. Situationen, in denen Personen den Drang zu kratzen verspüren, stellen zumeist eine Veränderung im Erleben von Sinnesempfindungen dar und werden so zum Ausgangspunkt für verändertes Verhalten. Aufgrund dessen ist es von großer Bedeutung, sich mit der neuronalen Grundlage von Pruritus zu beschäftigen. Zur Messung von Gehirnaktivität während Pruritus wird zumeist ein Pruritogen verabreicht, wobei Histamin die am häufigsten genutzte Substanz und der am besten untersuchte Pruritusmediator, auch in bildgebenden Studien, ist (Meng & Steinhoff, 2016; Pereira et al., 2018). Die Verabreichung von Pruritogenen bewirkt die Aktivierung der Rezeptoren in der Epidermis und Dermis. Der induzierte Reiz wird über langsame, nicht-myelinisierte C-Fasern aus der Peripherie in das zentrale Nervensystem weitergeleitet. Man unterscheidet mindestens zwei Typen von C-Fasern, histamin-sensitive und nicht-histamin-sensitive C-Fasern (Johanek et al., 2008; Schmelz et al., 1997; Schmelz et al., 2003). Im Rückenmark wird der Pruritus, ähnlich wie Schmerz, auf ein zweites Neuron verschaltet und dann kontralateral im Tractus Spinothalamicus

Lateralis zum Thalamus weitergeleitet. Im Thalamus findet die Verschaltung auf das dritte Neuron statt. Welche Nuclei des Thalamus bei Pruritus aktiviert sind, hängt vom verabreichten Pruritogen (z.B. Cowhage oder Histamin) ab (Davidson et al., 2012; Dhand & Aminoff, 2014; Papoiu et al., 2012).

Bildgebende Studien, in denen Pruritus-bezogene Gehirnaktivität bei gesunden Probanden untersucht wurde, nutzten vorrangig Histamin, aber auch Cowhage zur Pruritusinduktion. Sie konnten nachweisen, dass bei Pruritus verschiedene Großhirnareale aktiviert werden. So konnte eine gesteigerte Aktivierung des (prä-) frontalen Kortex, des supplementären Motorareals (SMA), der prämotorischen und primär motorischen Kortizes, der Inselregion, der primären und sekundären somatosensorischen Kortizes (SI und SII), der parietalen und cingulären Kortizes sowie des Präcuneus, Cerebellums und der Basalganglien gezeigt werden (Darsow et al., 2000; Herde et al., 2007; Hsieh et al., 1994; Ishiuji et al., 2009; Leknes et al., 2007; Mochizuki et al., 2007; Mochizuki & Kakigi, 2015; Papoiu et al., 2012; Schneider et al., 2008; Valet et al., 2008; Walter et al., 2005). In einigen Studien wurde hingegen eine Deaktivierung während der Pruritusinduktion bei gesunden Probanden gezeigt (Kleyn et al., 2012; Valet et al., 2008). Diese war interessanterweise auch in Regionen zu beobachten, in denen in anderen Studien eine erhöhte Gehirnaktivität während Pruritus beobachtet wurde: Eine Pruritus bedingte Reduktion der Gehirnaktivität wurde im Orbitofrontalkortex (OFC), medialen Frontalkortex, cingulären Kortex, Cerebellum, in den Basalganglien, in der Amygdala und im primären motorischen Kortex beobachtet (Herde et al., 2007; Kleyn et al., 2012; Valet et al., 2008).

Im Einklang mit der Annahme, dass Pruritus ähnlich wie Schmerz unterschiedliche Komponenten aufweist, eine sensorisch-diskriminative, kognitive, affektive und motivationale (Ikoma et al., 2006), findet eine Pruritusverarbeitung folglich in verschiedenen Gehirnarealen statt, welche wohlbemerkt natürlich nicht Pruritus spezifisch reagieren (Mochizuki & Kakigi, 2015). Mochizuki & Kakigi (2015) postulieren, dass das Erkennen und die Aufmerksamkeitslenkung auf den Pruritus mit einer Aktivierung des SII verbunden ist, die Einschätzung des Pruritus hinsichtlich seiner Lokalisation mit einer Aktivierung des SI einhergeht und dass diese beiden Gehirnareale zudem aktiv sind, wenn der Pruritus hinsichtlich seiner Intensität eingeschätzt wird. Die vordere Inselregion spielt nach Auffassung der Autoren eine

Rolle bei der emotionalen Verarbeitung des Pruritus, während der hintere Teil der Inselregion generell bei der Wahrnehmung von Körperempfindungen aktiviert zu sein scheint. Der cinguläre Kortex hingegen ist besonders dann von Bedeutung, wenn die Absicht besteht, eine motorische Handlung als Reaktion auf den Pruritus zu zeigen (Mochizuki & Kakigi, 2015).

Bildgebende Studien, in denen die Gehirnaktivierung von Patienten mit chronischem Pruritus mit der von gesunden Probanden während Histamin-induziertem Pruritus verglichen wurde (Ishiuji et al., 2009; Papoiu et al., 2014; Schneider et al., 2008), sind selten (Mochizuki et al., 2017) und zeigen kein einheitliches Bild: Während bei ND-Patienten in einer Studie während Histamin-induziertem Pruritus eine stärkere Aktivität des cingulären Kortex und des Präcuneus als bei hautgesunden Kontrollen beobachtet wurde (Ishiuji et al., 2009), zeigte eine andere Studie, in der regionsspezifische Analysen durchgeführt wurden, eine stärkere Aktivität im kontralateralen Thalamus, Nucleaus caudatus und Pallidum (Schneider et al., 2008). In einer weiteren Studie mit Patienten, die Pruritus aufgrund einer Nierenerkrankung im Endstadium aufwiesen, konnten diese patientenspezifischen Aktivitätssteigerungen im Gehirn während Histamin-induziertem Pruritus nicht beobachtet werden (Papoiu et al., 2014). Hier zeigte sich bei Patienten im Vergleich zu gesunden Kontrollprobanden aber während Cowhage-induziertem Pruritus eine reduzierte Aktivierung des SI, des superioren parietalen Kortex, des Präcuneus, der Inselregion und des anterioren cingulären Kortex (Papoiu et al., 2014).

Studien zur Gehirnaktivierung während pruritogen-frei induziertem Pruritus (siehe auch 1.5.2) wurden bislang nur bei gesunden Probanden (Holle et al., 2012; Mochizuki et al., 2013), Psoriasis (PS)-Patienten (Najafi et al., 2020) und Mäusen (Yu et al., 2017) durchgeführt. In Humanstudien zeigte sich während der Pruritusinduktion mittels visueller Stimuli eine Aktivierung in zum Teil den gleichen Gehirnarealen, die auch bei pruritogen-induziertem Pruritus aktiv sind. Bei der Präsentation eines Pruritus induzierenden Videos kam es zu einer vermehrten Aktivierung des SI sowie der präfrontalen und prämotorischen Kortizes (Holle et al., 2012), während die Betrachtung statischer Pruritusstimuli – allerdings unter gleichzeitiger Vorstellung, dass der Beobachtende sich in der Pruritus auslösenden Situation befindet – zu einer vermehrten Aktivierung des SMA, der Basalganglien, des Thalamus und des

Cerebellums führte (Mochizuki et al., 2013). In beiden Fällen war auch die Inselregion stärker aktiv (Holle et al., 2012; Mochizuki et al., 2013). Eine weitere Studie (Najafi et al., 2020) zeigte mittels funktioneller Konnektivitätsanalysen, dass während der Betrachtung von Videos sich kratzender Personen bei PS-Patienten im Vergleich zu hautgesunden Kontrollen einzelne Gehirnregionen, nämlich das Cerebellum, der Thalamus, das Cingulum, der untere Parietallappen, der mittlere Temporallappen und der Gyrus (para-) hippocampalis sowie der linguale und supramarginale Gyrus stärker miteinander verknüpft sind. Kritisch anzumerken an dieser Studie ist allerdings, dass die funktionelle Gehirnaktivität nur während der Präsentation eines Experimentalvideos (EVs), nicht aber während der Präsentation eines Kontrollvideos (KVs) erfasst wurde und dass bei sechs von 14 PS-Patienten durch die Präsentation des Videos kein Anstieg im Prurituserleben im Vergleich zum Baseline-Juckreiz zu verzeichnen war (Najafi et al., 2020).

Interessanterweise zeigte sich in einer tierexperimentellen Untersuchung (Yu et al., 2017) neben der Amygdala und Teilen der Basalganglien auch der Nucleus suprachiasmaticus nach visuell induziertem Pruritus aktiviert. Dieser spielte in Humanstudien während pruritogen- oder pruritogen-frei induziertem Pruritus bislang keine bedeutsame Rolle – ein Ergebnis, das allerdings kritisch zu betrachten ist, da in Folgestudien durch die Präsentation der gleichen visuellen Pruritusstimuli wie in der ersten Studie (Yu et al., 2017) bei Mäusen kein Kratzverhalten induziert werden konnte (Liljencrantz et al., 2017; Lu et al., 2019).

1.4 Forschungsstand zur Rolle psychologischer Faktoren bei Pruritus

Das biopsychosoziale Modell des chronischen Pruritus (Verhoeven et al., 2008) fasst zusammen, wie biologische, soziale und psychologische Faktoren interagierend Pruritus verändern. Es geht davon aus, dass – wie in Abbildung 1 veranschaulicht – internale (z.B. Persönlichkeitsfaktoren) oder externale Faktoren (z.B. kritische Lebensereignisse) sowohl alleine als auch in Kombination dazu führen, dass bestimmte kognitive Prozesse (z.B. katastrophisierende Gedanken), soziale Reaktionen (z.B. soziale Unterstützung oder Stigmatisierung) und Verhaltensweisen (z.B. automatisiertes Kratzen) angestoßen werden, welche ihrerseits physiologische Reaktionen triggern, die Pruritus dann reduzieren oder verstärken. Gemäß diesem Modell führt beispielsweise eine stressbedingte Cortisolausschüttung bei Mäusen zu

einer Mastzelldegeneration, welche mit erhöhter Histaminausschüttung assoziiert ist (Liezmann et al., 2011). Auch lässt sich bei ND-Patienten nach mechanischer Stimulation der Haut durch Kratzen eine vermehrte lokale Sekretion pruritogener Substanzen wie Serotonin beobachten, die Pruritus verstärken kann (Leung et al., 2004). Zudem wurde gezeigt, dass der Zusammenhang von Stress und basaler Pruritusintensität bei ND-Patienten durch Pruritus-bezogene Krankheitsbewältigung mediiert wird (Schut et al., 2015c): Stress geht demnach nur dann mit intensiverem Pruritus einher, wenn er mit einem wahrgenommenen Verhaltenskontrollverlust und katastrophisierenden Gedanken bezüglich Pruritus assoziiert ist.

Auf einige der im biopsychosozialen Modell angesprochenen Faktoren wird im Folgenden genauer eingegangen, da sie in den Studien dieser Habilitationsschrift in ihrer Rolle als mögliche Moderatoren für pruritogen-frei induzierten Pruritus untersucht wurden. Bei diesen genauer zu betrachtenden, psychologischen Faktoren handelt es sich um Persönlichkeitsfaktoren, Selbstaufmerksamkeit, Angst, Depression und die Erwartungshaltung.

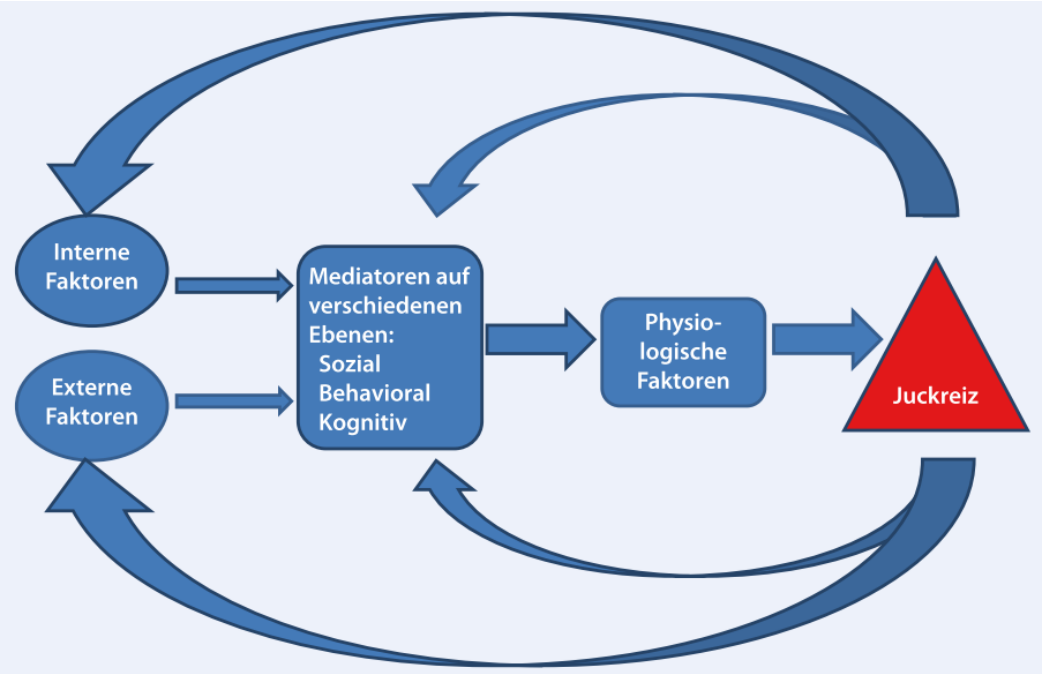

Abbildung 1. Biopsychosoziales Modell des chronischen Pruritus (Abbildung aus Schut & Kupfer, 2013; modifiziert nach Verhoeven et al., 2008; mit Genehmigung von Springer Nature)

1.4.1 Persönlichkeit

Für das Konstrukt Persönlichkeit existieren unterschiedliche Definitionen (Margraf-Stiksrud, 2019). Laut Gordon Allport, einem Vertreter des eigenschaftsorientierten Ansatzes der Persönlichkeitsforschung (Maltby et al., 2011), handelt es sich bei Persönlichkeit um „die dynamische Ordnung derjenigen psychophysischen Systeme im Individuum, die sein Verhalten und Denken determinieren“ (Allport & Bracken, 1970; zitiert nach Maltby et al., 2011, S. 40).

Persönlichkeitspsychologischen Untersuchungen wird üblicherweise das Fünf-Faktoren-Modell der Persönlichkeit zugrunde gelegt. Dieses geht davon aus, dass es fünf Persönlichkeitsfaktoren gibt, über die sich sehr gut die menschliche Persönlichkeit beschreiben lässt. Bei den fünf Faktoren handelt es sich um Offenheit für neue Erfahrungen, Gewissenhaftigkeit, Extraversion, Verträglichkeit und Neurotizismus (Borkenau & Ostendorf, 2008; Pervin et al., 2005; Stemmler, 2010). Personen, die hohe Werte auf der Skala Offenheit für neue Erfahrungen aufweisen, kennzeichnen sich dadurch, dass sie neugierig, kreativ, offen für Fantasie, Ästhetik, Gefühle, Handlungen und Ideen sind und viele unterschiedliche Interessen haben. Hohe Werte auf der Skala Gewissenhaftigkeit gehen mit Pflichtbewusstsein, Fleiß, Zuverlässigkeit, Ehrgeiz, Ordentlichkeit, Ausdauer, Selbstdisziplin und Besonnenheit einher. Ein hohes Ausmaß an Extraversion ist gekennzeichnet durch Geselligkeit, Aktivität, Redseligkeit, Lebenslust, Durchsetzungsfähigkeit und Erlebnishunger. Personen mit hohen Werten auf der Skala Verträglichkeit sind bescheiden, gutherzig, kooperativ, selbstlos, freundlich und entgegenkommend. Ein hohes Maß an Neurotizismus ist gekennzeichnet durch emotionale Instabilität, Ängstlichkeit, schnelle Reizbarkeit, hohe Verletzlichkeit und Angespanntheit (Borkenau & Ostendorf, 2008; Maltby et al., 2011; Pervin et al., 2005; Stemmler, 2010). Es existieren deutsch- und englischsprachige, validierte Fragebögen, mit Hilfe derer die „Big-Five“ der Persönlichkeit messbar sind (z.B. Borkenau & Ostendorf, 2008; Costa & McCrae, 2000).

In einigen, zum Teil älteren Arbeiten wurde behauptet, dass sich Patienten mit juckenden Hauterkrankungen von Hautgesunden in ihrer Persönlichkeit unterscheiden und sogar ein bestimmtes Persönlichkeitsprofil aufweisen (Ahmar & Kurban, 1976; Kim et al., 2006; Obermayer, 1949; Rogerson, 1947). Bezüglich der Big-Five-Persönlichkeitsfaktoren zeigten Studien, dass ND-Patienten höhere Werte in

Neurotizismus-Skalen aufwiesen als hautgesunde Kontrollen (Ahmar & Kurban, 1976) oder Normstichproben (White et al., 1990). Damit korrespondieren Befunde, nach denen ND-Patienten angaben, ängstlicher und weniger durchsetzungsfähig zu sein als hautgesunde Kontrollen (Ginsburg et al., 1993). Auch Magin et al. (2008) konnten bei Patienten mit ND, Akne und PS höhere Neurotizismus-Werte zeigen. Eine Studie von Jordan & Whitlock (1972), in der ND-Patienten mit Patienten mit anderen Erkrankungen (Hepatitis, neurologische Erkrankungen, Bluthochdruck, Herzerkrankungen, Schilddrüsenüberfunktion oder Symptome unklarer Ursache) verglichen wurden, konnte bei ND-Patienten ebenfalls mit einem Messinstrument höhere Neurotizismus-Werte finden, nicht aber mit dem zweiten parallel eingesetzten Fragebogen. Anzumerken ist an dieser Stelle, dass in keiner der Studien alle Big-Five-Persönlichkeitsfaktoren erfasst wurden, sondern lediglich Extraversion und Neurotizismus (Ahmar & Kurban, 1976; Jordan & Whitlock, 1972; Magin et al., 2006; White et al., 1990). Alle Big-Five-Faktoren wurden in einer aktuellen Studie (Najafi et al., 2020) erfasst, in der sich zeigte, dass hautgesunde Kontrollen höhere Werte in der Skala “Offenheit für neue Erfahrungen” aufwiesen als PS-Patienten. Allerdings lässt auch diese Studie keine Aussage zum direkten Zusammenhang zwischen Persönlichkeitsfaktoren und Pruritus zu.

Studien, die den Anspruch haben, Zusammenhänge zwischen Pruritus und Persönlichkeitsfaktoren zu identifizieren, sind aber insofern notwendig, da sie Rückschlüsse darauf ermöglichen, ob Patienten mit einem bestimmten Persönlichkeitsprofil, Pruritus intensiver wahrnehmen und in Folge dessen ein ausgeprägteres Kratzverhalten in Pruritus auslösenden Situationen zeigen als Personen mit gegenteiligem Persönlichkeitsprofil. Diese Erkenntnisse sind notwendig, um genau diesen Personengruppen dann gezielt verhaltensregulierende Trainings anbieten zu können.

Forschungsarbeiten, in denen korrelative Zusammenhänge zwischen Pruritus und Faktoren des Big-Five-Modells der Persönlichkeit untersucht wurden, existieren bereits (Bartels et al., 2014; Holle et al., 2012; Najafi et al., 2020; Psouni, 2004; van Laarhoven et al., 2010; Verhoeven et al., 2006; Yilmaz et al., 2016). Viele der Studien wurden aber bei Hautgesunden durchgeführt (Bartels et al., 2014; Holle et al., 2012; Psouni, 2004; van Laarhoven et al., 2010). Sie liefern zudem ein uneinheitliches Bild:

Es zeigten sich teilweise positive Zusammenhänge zwischen Pruritusintensität und Neurotizismus (Holle et al., 2012; Psouni, 2004) bzw. Offenheit für neue Erfahrungen (Psouni, 2004) sowie negative Zusammenhänge zwischen Verträglichkeit und Pruritus (Psouni, 2004). Extraversion hing in einem Fall negativ (Bartels et al., 2014) und in einem Fall positiv (Psouni, 2004) mit induziertem Pruritus zusammen.

Bei Patienten mit Pruritusproblematik, in dem Fall ND- und PS-Patienten, ließ sich ein positiver Zusammenhang zwischen Neurotizismus und basal vorliegendem Pruritus und selbstberichtetem Kratzverhalten feststellen (Verhoeven et al., 2006). Bei Patienten mit Pruritus im äußeren Gehörgang war Extraversion signifikant negativ mit Pruritus assoziiert (Yilmaz et al., 2016). In der aktuellsten Studie zum Zusammenhang zwischen Pruritus und Persönlichkeit, in die auch Patienten mit Pruritusproblematik eingeschlossen wurden, zeigten sich hingegen weder bei PS-Patienten noch bei Hautgesunden signifikante Zusammenhänge zwischen visuell induziertem Pruritus und den Big-Five-Persönlichkeitsfaktoren (Najafi et al., 2020).

Anzumerken ist an dieser Stelle, dass nur in wenigen Arbeiten Pruritus realitätsnah, mittels (audio-)visueller Stimuli, induziert wurde (Holle et al., 2012; Najafi et al., 2020). Auch wurden – wie bereits erwähnt – nicht immer alle Persönlichkeitsfaktoren des Big-Five-Persönlichkeitsmodells erfasst (z.B. Verhoeven et al., 2006). Weiterhin ist auffällig, dass die Zusammenhänge zwischen Persönlichkeitsfaktoren und Pruritus bei Patienten mit Pruritusproblematik und hautgesunden Probanden bislang erst einmal vergleichend gegenüber gestellt wurden (Najafi et al., 2020). Gänzlich unbetrachtet blieb der Zusammenhang zwischen Persönlichkeit und tatsächlich beobachtetem Kratzverhalten in der Gruppe der Hautpatienten.

Es drängen sich an dieser Stelle somit zwei Forschungsfragen auf, die es zu beantworten gilt: Zum einen ist von Interesse, ob sich die Zusammenhänge zwischen Persönlichkeitsfaktoren und Pruritus zwischen Patienten mit juckenden Hauterkrankungen und hautgesunden Kontrollprobanden unterscheiden. Des Weiteren stellt sich die Frage nach dem Zusammenhang zwischen Kratzverhalten und Persönlichkeitsfaktoren, besonders für die Gruppe der Patienten mit Pruritusproblematik. Die zuletzt genannte Frage zum Kratzverhalten blieb in der bislang vorhandenen Literatur gänzlich unbeantwortet.

1.4.2 Selbstaufmerksamkeit

Bei Selbstaufmerksamkeit handelt es sich einerseits um einen experimentell erzeugbaren Zustand, andererseits um eine Disposition, die menschliches Verhalten verändert (Filipp & Freudenberg, 1989). Es wird zwischen privater und öffentlicher Selbstaufmerksamkeit unterschieden. Während hohe Werte in dem Konstrukt „Private Selbstaufmerksamkeit“ illustrieren, dass eine Person insbesondere den nur ihr selbst zugänglichen, also nicht beobachtbaren Faktoren, wie Körpersensationen, Absichten und Gefühlen, Aufmerksamkeit schenkt, veranschaulichen hohe Werte auf der Skala „Öffentliche Selbstaufmerksamkeit“, dass Personen viel Aufmerksamkeit den Dingen, die um sie herum passieren, widmen. So würden Personen mit hohen Werten auf dieser Skala besonders viel Aufmerksamkeit darauf legen, wie sie aufgrund ihres äußeren Auftretens und Verhaltens auf andere wirken und was andere von ihnen halten (Filipp & Freudenberg, 1989). Selbstverständlich kann eine Person gleichzeitig hohe Werte in privater und öffentlicher Selbstaufmerksamkeit aufweisen.

In einer qualitativen Studie ergaben sich Hinweise darauf, dass vermehrte Selbstaufmerksamkeit eine bedeutsame Folge von Akne ist (Magin et al., 2006). Ebenso wurde quantitativ ermittelt, dass Patienten mit Akne, PS und ND höhere Werte in der Skala „Öffentliche Selbstaufmerksamkeit“ aufweisen als hautgesunde Kontrollen (Magin et al., 2008b). Anzumerken ist, dass in der letztgenannten Studie die Facette „Private Selbstaufmerksamkeit“ nicht bestimmt wurde. Eine erhöhte private Aufmerksamkeit, speziell auf körperliche Symptome, zeigte sich bei ND-Patienten im Vergleich zu hautgesunden Kontrollen in einer Studie (Oh et al., 2010), in der allerdings das Symptom Pruritus nicht erfasst wurde. Signifikant positive Korrelationen zwischen der Intensität von experimentell induziertem Pruritus und Vigilanz für körperliche Symptome konnten bei hautgesunden Personen beobachtet werden (van Laarhoven et al., 2010). In einer weiteren Studie, in die Patienten mit unterschiedlichen Hauterkrankungen eingeschlossen wurden, ergaben sich signifikante, positive Zusammenhänge zwischen basal gemessenem Pruritus und allgemeiner Selbstaufmerksamkeit (Lotfi et al., 2015).

Die Frage, ob Selbstaufmerksamkeit bei Patienten mit Hauterkrankungen ein Prädiktor für das Ausmaß von audio-visuell induziertem Pruritus und/ oder Kratzverhalten ist,

blieb allerdings bislang gänzlich unbeantwortet. Ihr wurde deshalb in Studien, die in diese Habilitationsschrift eingingen, nachgegangen.

1.4.3 Angst, Depression

Die überwiegende Mehrheit von Patienten, die eine Hautarztpraxis aufsucht, berichtet von einer mit Pruritus einhergehenden emotionalen Belastung (Kopyciok et al., 2016). Angst und Depression stellen psychologische Faktoren dar, die bei Patienten mit juckenden Hauterkrankungen eine wesentliche Rolle spielen. Ängstlichkeit ist zudem ein Merkmal, das Personen mit hohen Neurotizismus-Werten kennzeichnet (Pervin et al., 2005) – also hohen Ausprägungen in dem Persönlichkeitsfaktor, der in einigen Studien (Holle et al., 2012; Psouni, 2004) wie oben beschrieben mit Pruritusintensität korreliert war. Eine Reihe von Studien zeigt passend dazu, dass Patienten mit chronischen, juckenden Hauterkrankungen wie ND, PS, Prurigo nodularis, Lichen Simplex oder Urtikaria höhere Depressions- und/ oder Angstwerte aufweisen als (haut-)gesunde Kontrollprobanden (Conrad et al., 2008; Devrimci-Ozguven et al., 2000; Konda et al., 2015; Konuk et al., 2007; Silverberg et al., 2019), auch wenn diese Unterschiede nicht immer signifikant sind (Sheehan-Dare et al., 1990). Bedeutsam ist in diesem Kontext, dass Dermatologen die Prävalenz von Angst und Depression bei Patienten mit Hauterkrankungen unterschätzen (Dalgard et al., 2018).

In einer groß angelegten europäischen Multi-Center-Studie (Dalgard et al., 2020) zeigte sich weiterhin, dass der Zusammenhang zwischen dem Vorliegen einer Hauterkrankung und einer depressiven Symptomatik signifikant davon mitbestimmt wird, ob die Hauterkrankung mit Pruritus einhergeht: Die Wahrscheinlichkeit an einer Depression zu leiden, war bei Patienten mit Pruritus im Vergleich zu Patienten ohne Pruritus um ca. 50% erhöht. Auch die Punktprävalenz von klinisch bedeutsamer Angst unterschied sich zwischen Patienten mit Hauterkrankungen mit und ohne Pruritus. Bei Patienten mit Pruritus lag sie bei 21,4%, während 12,3% der Patienten ohne Pruritus eine klinisch relevante Angststörung aufwiesen, wobei der Unterschied nicht statistisch signifikant wurde (Dalgard et al., 2020). Darüber hinaus zeigen Studien, in denen Patienten mit Hauterkrankungen bzw. Patienten mit Polycythaemia vera mit und ohne Pruritus verglichen wurden, signifikant erhöhte Angst-, aber nicht Depressionswerte

bei Patienten mit Pruritus im Vergleich zu denjenigen ohne Pruritus (Lelonek et al., 2018; Marron et al., 2016).

Neben den bisherigen Studien, die sich lediglich mit dem gemeinsamen Auftreten von Pruritus und Angst bzw. Depression beschäftigten, liegen weitere Querschnitts-Studien vor, in denen Korrelationen zwischen der Pruritus*intensität* und der Ausprägung einer depressiven bzw. ängstlichen Symptomatik bei Patienten mit Pruritus untersucht wurden: Hier zeigte sich sowohl bei Hämodialyse-Patienten, Patienten mit urämischem Pruritus, Handekzem, PS, ND und Urtikaria ein signifikant positiver Zusammenhang zwischen der Pruritusintensität und dem Grad der Depressivität (Conrad et al., 2008; Gupta et al., 1988; Gupta et al., 1994; Gupta & Gupta, 1999; Lotfi et al., 2015; Mrowietz et al., 2015; Ozen et al., 2018; Reich et al., 2010; Silverberg et al., 2019; Silverberg et al., 2020) und/ oder dem Grad der Angst (Boehm et al., 2012; Lotfi et al., 2015; Mrowietz et al., 2015; Oh et al., 2010; Rasul et al., 2016; Sheehan-Dare et al., 1990; Silverberg et al., 2019; Silverberg et al., 2020; Weiss et al., 2016; Zachariae et al., 2012). Bei Patienten mit Prurigo nodularis ließ sich hingegen kein Zusammenhang zwischen Depressivität und Pruritusintensität finden (Konda et al., 2015). Reich et al. (2017) entwickelten einen Fragebogen zur umfassenden Erfassung von Pruritus, welcher neben Items zur Intensität auch Items zur Ausbreitung des Pruritus, seiner Häufigkeit und Dauer, seinem Einfluss auf tägliche Aktivitäten und die Stimmung und das Kratzverhalten beinhaltet. In der Validierungsstudie des Fragebogens zeigten sich bei Patienten mit juckenden Hauterkrankungen signifikante Korrelationen zwischen dem für Pruritus ermittelten Globalwert und Angst/ Depression, nicht aber zwischen der Pruritusintensität alleine und Angst/ Depression (Reich et al., 2017).

Bedeutsam ist, dass die bislang zitierten Studien, sich alle mit dem Zusammenhang von *basal gemessener Angst/ Depression bzw. basal vorliegendem Pruritus* beschäftigten. Studien, die den Effekt von Angst/ Depression auf experimentell induzierten Pruritus bei Patienten mit Pruritusproblematik betrachten, liegen noch nicht vor. Ob basal gemessene Angst und Depression Prädiktoren für pruritogen-frei, audio-visuell induzierten Pruritus bei Patienten mit Hauterkrankungen darstellen, wurde mit den Studien 3-5, die in diese Habilitationsschrift eingingen, somit erstmals analysiert.

1.4.4 Erwartungshaltung

Es ist vorstellbar, dass neben den bereits genannten psychologischen Faktoren auch die Erwartung, mit der Patienten an Pruritus induzierende Situationen herantreten, die Intensität des Pruritus und das resultierende Kratzverhalten mitbestimmt. Hierzu lässt sich festhalten, dass die Rolle von Erwartungen – oftmals erzeugt über verbale Suggestionen – für die Wahrnehmung von Pruritus bislang wesentlich weniger intensiv beforscht wurde als die Rolle von Erwartungen im Kontext der Schmerzwahrnehmung (Evers et al., 2014). Erst in den letzten zehn Jahren steigt die Anzahl der Studien, die sich mit Erwartungseffekten auf klinisch bedingten oder experimentell induzierten Pruritus beschäftigen (Evers et al., 2019). In einer Metaanalyse (van Laarhoven et al., 2015) zeigte sich, dass die Gabe eines Placebos – typischerweise mit der Erwartung einer Symptomreduktion einhergehend – Pruritus bei Patienten mit Hauterkrankungen signifikant reduziert. Für den klinischen Kontext ist zudem wichtig, dass sich in Abhängigkeit von der Methode, mit der wirkstoffhaltige Substanzen appliziert werden, die Erwartung bezüglich ihrer Effektivität verändert: Personen erwarten eine größere Pruritusreduktion bei topischer Applikation der Wirkstoffe im Vergleich zu oral gegebenen oder injizierten Substanzen (Peerdeman et al., 2018).

In Studien, in denen Pruritus *im experimentellen Setting* mittels unterschiedlicher Methoden induziert wurde, zeigten sich ebenfalls, allerdings nicht durchgängig, Erwartungseffekte auf Pruritus. In diesen Studien wurden sowohl der Placebo-Effekt (reduzierter experimentell induzierter Pruritus durch vorherige Erwartungsänderung) als auch der Nocebo-Effekt (intensiver experimentell induzierter Pruritus durch vorherige Erwartungsänderung) untersucht (Bartels et al., 2018; Bartels et al., 2017a; Bartels et al., 2017b; Evers et al., 2014; Evers et al., 2019; Meeuwis et al., 2018; Meeuwis et al., 2019; Stumpf et al., 2016; van de Sand et al., 2018; van Laarhoven et al., 2011). Größtenteils wurden in diese Studien hautgesunde Probanden ohne Pruritusproblematik eingeschlossen (Bartels et al., 2018; Bartels et al., 2017a; Bartels et al., 2017b; Evers et al., 2014; Evers et al., 2019; Meeuwis et al., 2018; Meeuwis et al., 2019; Stumpf et al., 2016; van de Sand et al., 2018; van Laarhoven et al., 2011): Die erste (van Laarhoven et al., 2011) einer ganzen Reihe Placebo-/ Nocebo-Studien (Bartels et al., 2018; Bartels et al., 2017a; Bartels et al., 2017b; Meeuwis et al., 2018; Meeuwis et al., 2019; Peerdeman et al., 2015; Peerdeman et al., 2016; Peerdeman et

al., 2018) zeigte Effekte verbaler Suggestionen auf induzierten Pruritus: Gesunde Probandinnen, denen suggeriert wurde, dass die Pruritusstimuli bei den meisten Pruritus und nur selten Schmerz induzieren (Nocebo-Bedingung), zeigten nach Applikation von Pruritusstimuli eine höhere Pruritusintensität als gesunde Probandinnen der Kontrollbedingung, denen suggeriert wurde, dass die verabreichten Stimuli nur selten Pruritus oder Schmerz induzieren. In Übereinstimmung mit den Ergebnissen dieser Studie (van Laarhoven et al., 2011) zeigte eine Folgestudie einen zumindest tendenziell signifikanten Nocebo-Effekt bezüglich Pruritus, welcher durch verbale Suggestionen hervorgerufen wurde (Bartels et al., 2014). Die Folgestudie (Bartels et al., 2014) zeigte weiterhin, dass eine Veränderung der Erwartung bezüglich Pruritusstimuli durch verbale Suggestionen in Kombination mit klassischer Konditionierung zu höheren Nocebo-Effekten führte als eine Kontrollbedingung, in der weder eine Konditionierung auf Pruritusstimuli erfolgte noch die Probanden verbal Informationen zu den applizierten Pruritusstimuli erhielten.

Weitere Studien zu Effekten von Erwartungshaltung auf Pruritus (Meeuwis et al., 2018; Meeuwis et al., 2019; Schaefer et al., 2016) widmeten sich darüber hinaus der Frage, ob auch trotz des Wissens, dass ein Placebo verabreicht wird (Meeuwis et al., 2019; Schaefer et al., 2016), oder trotz des Wissens, dass Erwartungen Pruritus nach Applikation einer Pruritus induzierenden Substanz verändern (Meeuwis et al., 2018), ein Placebo-Effekt bezüglich Pruritus auftritt. Dies ist nicht der Fall.

Studien, die Effekte von Erwartungen auf Pruritus bei *Patienten mit chronischem Pruritus* untersuchten, sind selten (Hermanns & Scholz, 1992; Napadow et al., 2015; Scholz & Hermanns, 1994): Es zeigte sich bei ND-Patienten, dass dramatisierende Informationen bezüglich eines Histamin-Prick-Tests zu intensiverem Pruritus führten als beschwichtigende Informationen (Hermanns & Scholz, 1992; Scholz & Hermanns, 1994). Darüber hinaus berichteten ND-Patienten signifikant intensiveren Pruritus nach Applikation von Kochsalzlösung, wenn diese für ein Allergen gehalten wurde, als wenn sie als „Tropfen Wasser“ ausgegeben wurde (Napadow et al., 2015).

Ob eine veränderte Erwartung bezüglich Pruritusstimuli auch Effekte auf die *Hautreaktion oder das Kratzverhalten* hat, war Gegenstand nur weniger Studien (Bartels et al., 2018; Darragh et al., 2013; Darragh et al., 2015; Scholz & Hermanns,

1994; Stumpf et al., 2016). Es zeigte sich, dass katastrophisierende Informationen bezüglich Pruritusstimuli sowohl bei ND-Patienten (Hermanns & Scholz, 1992) als auch bei hautgesunden Probanden (Stumpf et al., 2016) eine größere Histamin-induzierte Quaddel hervorrief als relativierende (Hermanns & Scholz, 1992) bzw. realistische Informationen (Stumpf et al., 2016) bezüglich der Pruritusstimuli. In zwei weiteren Studien wurden ebenfalls Erwartungseffekte auf die Größe einer Histamin-induzierten Quaddel bei hautgesunden Kontrollprobanden untersucht (Darragh et al., 2013; Darragh et al., 2015). Es zeigte sich, dass die Information, dass es sich bei der vor Pruritusinduktion aufgetragenen wirkungslosen Substanz um eine den Pruritus lindernde Salbe handelte, keine Effekte auf die Veränderung der Quaddelgröße hatte. In weiteren Studien zeigte sich, dass Vorinformationen zu Pruritusstimuli auch keinen Effekt auf den Wunsch zu kratzen hatten (Stumpf et al., 2016) und dass nach Konditionierung auf einen bestimmten Reiz bei Präsentation desselben zwar intensiverer Pruritus auftrat, parallel aber nicht mehr Kratzbewegungen oder eine längere Kratzdauer zu beobachten waren (Bartels et al., 2018).

Zusammenfassend lässt sich an dieser Stelle festhalten, dass fast alle Studien aus diesem Bereich lediglich hautgesunde Probanden und keine Patienten mit chronischem Pruritus einschlossen. Die Untersuchung der Zusammenhänge zwischen Pruritus/ Kratzverhalten und Erwartungen ist aber gerade bei Patienten mit chronischem Pruritus sinnvoll und notwendig, da sich hieraus ggf. Ansätze für eine gewinnbringende Kommunikation mit den Patienten ableiten lassen. Der Frage, inwiefern Vorinformationen zu Pruritus auslösenden Stimuli induzierten Pruritus und induziertes Kratzverhalten bei Patienten mit klinisch bedingtem Pruritus verändern, wird deswegen ebenfalls im Rahmen dieser Arbeit nachgegangen.

1.4.5 Offene Fragen zu psychologischen Variablen und Pruritus

Die meisten bislang durchgeführten Studien, in denen Persönlichkeit, Angst, Depression, Selbstaufmerksamkeit und die Erwartungshaltung als Pruritus moderierende Faktoren untersucht wurden, schlossen entweder lediglich *gesunde* Probanden ein oder *Pruritus* wurde *nicht experimentell induziert*. Dabei ließen sich genau aus derartigen Untersuchungen Erkenntnisse ableiten, welche psychologischen Faktoren die Entstehung von Pruritus begünstigen und durch welche psychologischen

Methoden ihm möglicherweise zielgenau begegnet werden kann. Das vorrangige Ziel der Studien, die dieser Habilitationsschrift zugrunde liegen, war es deswegen, psychologische Moderatoren für experimentell induzierten Pruritus bei Patienten mit chronischem Pruritus zu identifizieren – immer unter gleichzeitiger Betrachtung derselben Zusammenhänge bei hautgesunden Kontrollprobanden.

1.5 Methoden zur Pruritusinduktion im Labor

Um Assoziationen zwischen psychologischen Variablen und Pruritus bei Patienten mit chronischem Pruritus und gesunden Kontrollprobanden mit möglichst hoher interner Validität untersuchen zu können, ist es u.a. notwendig, Pruritus im Labor unter standardisierten Bedingungen zu induzieren. Hierfür stehen unterschiedliche Methoden zur Verfügung (Najafi et al., 2021). Diese lassen sich dahingehend unterscheiden, ob eine pruritogene, also Pruritus induzierende Substanz appliziert wird oder nicht (Najafi et al., 2021). In diesem Kapitel wird zunächst auf pruritogen-gebundene und anschließend auf pruritogen-freie Methoden der Pruritusinduktion eingegangen. Das Kapitel schließt mit einer Zusammenstellung der Vor- und Nachteile der pruritogen-freien Methode im Vergleich zu pruritogen-gebundenen Methoden der Pruritusinduktion ab.

1.5.1 Pruritogen-gebundene Methoden

Innerhalb der pruritogen-gebundenen Pruritusinduktionsmethoden lässt sich zwischen Methoden unterscheiden, mittels welcher mechano-insensitive C-Fasern oder polymodale C-Fasern aktiviert werden (LaMotte et al., 2014; Namer et al., 2008). Histamin stellt einen Pruritus induzierenden Stoff dar, der bei Menschen hauptsächlich über mechano-insensitive C-Fasern weitergeleitet wird (LaMotte et al., 2014). Cowhage hingegen gilt als Stoff, der über polymodale C-Fasern transportiert wird (LaMotte et al., 2014). Pruritusinduktion mittels dieser beiden Pruritogene wird im Folgenden etwas genauer betrachtet, da diese beiden Stoffe besonders in den letzten Jahren oft im Bereich der Pruritusforschung und auch in der eigenen Arbeitsgruppe angewendet wurden.

1.5.1.1 Histamin

Histamin ist das bislang am meisten untersuchte Pruritogen und gilt als der „Gold-Standard“ der Pruritusinduktion (Andersen et al., 2015; LaMotte et al., 2014). Histamin stimuliert lokal H1-Rezeptoren und bewirkt eine erhöhte Gefäßdurchlässigkeit, Vasodilatation sowie Mastzelldegranulation in der Haut (Ashina et al., 2015; Pereira et al., 2020). Klinisch lassen sich nach Histamin-Gabe nicht nur Pruritus, sondern auch Rötung und Quaddeln beobachten (Darsow et al., 1996). Histamin kann auf unterschiedlichen Wegen appliziert werden, typischerweise mittels Haut-Prick (Darsow et al., 1996; Darsow et al., 2000; Walter et al., 2005), Iontophorese (Namer et al., 2008; Papoiu et al., 2012; Papoiu et al., 2011a) oder über inaktivierte Cowhage-Härchen (Hartmann et al., 2015; Kosteletzky et al., 2009; Sikand et al., 2009). Hierbei ist zu beachten, dass die Anwendung verschiedener Histamin-Applikations-Methoden (Darsow et al., 1996) und Dosierungen (Magerl et al., 1990; Sikand et al., 2009) Unterschiede in der induzierten Pruritusintensität bedingt. Bei der Pruritusinduktion mittels Histamin-Iontophorese wird üblicherweise (Papoiu et al., 2012; Papoiu et al., 2011a) eine 1%-Histamin-Lösung in 2%igem Methylzellulose-Gel verwendet – so auch in den eigenen Studien. Hierbei macht man sich zunutze, dass Histamin die oberste Schicht der Haut durchdringt, wenn ein schwacher elektrischer Strom an der Stelle, an der die Histamin-Lösung auf die Haut gebracht wird, geleitet wird (Magerl et al., 1990).

1.5.1.2 Cowhage

Neben Histamin werden auch die Fasern der tropischen Pflanze Cowhage („*Mucuna pruriens*“) zur Induktion von Pruritus genutzt. Dass die Fasern dieser Pflanze Pruritus erzeugen, wurde erstmals Ende des 18. Jahrhunderts in der Literatur beschrieben (Chamberlaine 1784, zitiert nach Shelley & Arthur, 1955b) und Mitte des 19. Jahrhunderts genauer untersucht (Shelley & Arthur, 1955a; Shelley & Arthur, 1955b; Shelley & Arthur, 1957). In den letzten 15 Jahren haben Wissenschaftlerinnen und Wissenschaftler diese Art der Pruritusinduktion neu entdeckt und genutzt, um nicht-histaminergen Pruritus zu induzieren. Cowhage ist als Pruritogen von großem Interesse, da sich Pruritus bei chronischen Hauterkrankungen wie ND nicht immer durch die Gabe von Antihistaminika reduzieren lässt (LaMotte et al., 2014; Weisshaar et al., 2019). Bei Pruritusinduktion mittels Cowhage bindet die Protease „Mucunain“ der Cowhage-Fasern an Proteinase-aktivierende Rezeptoren (PAR-) 2 und 4 sowie an

Mas-bezogene G-Protein bindende Rezeptoren (MRGPRs) und aktiviert so nicht-histaminerge, mechano- und Hitze-sensitive C-Fasern (Namer et al., 2008; Pereira et al., 2020). Zur Pruritusinduktion werden die Fasern üblicherweise 45 Sekunden mit kreisenden Bewegungen in die Haut gerieben (Papoiu et al., 2012; Papoiu et al., 2011a) oder mittels Druck auf einen Watteapplikator, auf dem sich Cowhage-Fasern befinden, in die Haut gestochen (Kosteletzky et al., 2009; Sikand et al., 2009).

1.5.1.3 Vergleich von Histamin- und Cowhage-induziertem Pruritus

Die Forschung hat es sich in den vergangenen 10 Jahren zur Aufgabe gemacht, Pruritus, induziert mittels Cowhage und Histamin, in Vergleichsstudien einander gegenüber zu stellen (Andersen et al., 2017; Hartmann et al., 2015; Hawro et al., 2019; Kosteletzky et al., 2009; Papoiu et al., 2012; Papoiu et al., 2011a; Sikand et al., 2009; Sikand et al., 2011). Hierbei fanden sie teilweise Unterschiede hinsichtlich der *Intensität* (Papoiu et al., 2011a) und *Qualität* (Hawro et al., 2019; Kosteletzky et al., 2009) des induzierten Pruritus, welche auch mit der Dosierung von Histamin zusammenzuhängen scheinen. Pruritus, induziert durch in die Haut eingeriebene Cowhage-Härchen, war in einer Studie intensiver als mittels Histamin-Iontophorese induzierter Pruritus, wenn eine 1%ige Histamin-Lösung appliziert wurde. Ein Summationseffekt ergab sich nicht: Pruritus, der zugleich mittels Histamin-Iontophorese sowie durch das Einreiben von Cowhage-Fasern induziert wurde, war also nicht intensiver als durch Cowhage allein induzierter Pruritus (Papoiu et al., 2011a). Dieses Ergebnis galt sowohl für Patienten mit chronischem Pruritus als auch für hautgesunde Kontrollprobanden (Papoiu et al., 2011a). In anderen Studien, in denen Pruritus bei gesunden Probanden mittels Histamin auf inaktiven Cowhage-Härchen oder durch aktive Cowhage-Härchen hervorgerufen wurde, unterschieden sich die hervorgerufenen Pruritusintensitäten durch Cowhage und Histamin nicht voneinander (Sikand et al., 2009): Stattdessen ließ sich beobachten, dass Histamin in der Dosis 10mg/ml zu Pruritus ähnlicher Intensität führte wie die Applikation einzelner Cowhage-Härchen.

Bezüglich der Qualität des induzierten Pruritus zeigten sich in einer Studie (Kosteletzky et al., 2009) bei nur 3 von 24 untersuchten Pruritusqualitäten signifikante Unterschiede: Der durch Applikation von Cowhage-Härchen induzierte Pruritus wurde als stechender, schärfer und spitzer empfunden als Pruritus, der mittels inaktivierten

Cowhage-Härchen, auf die eine 1%ige Histamin-Lösung aufgetragen worden war, induziert wurde. Dieses Ergebnis deckt sich mit Ergebnissen anderer Studien (Hawro et al., 2019; Namer et al., 2008). In diesen führte bei gesunden Probanden zum einen das Einreiben von aktiven Cowhage-Härchen zu intensiverem Brennen und Pieksen als mittels Skin-Prick-Test appliziertes Histamin in der Dosis 10mg/ml (Hawro et al., 2019). Zum anderen beschrieben Probanden Cowhage-induzierten Pruritus als brennend und stechend und als sehr gut lokalisierbar, wohingegen Pruritus induziert über 1%ige Histamin-Lösung, appliziert mittels Iontophorese, als „purer Pruritus“ beschrieben wurde, der größere Bereiche betraf (Namer et al., 2008). Zudem erzeugte Histamin eine (größere) Quaddel im Vergleich zu Cowhage (Hartmann et al., 2015; Hawro et al., 2019; Kosteletzky et al., 2009; Sikand et al., 2009).

1.5.2 Pruritogen-freie Methoden

In den letzten zehn Jahren wurde nicht nur der Vergleich von Histamin- und Cowhage-induziertem Pruritus immer populärer, sondern auch eine pruritogen-freie Induktion von Pruritus und Kratzverhalten. Möglich ist diese sowohl über eine kombinierte Präsentation auditiver und visueller Pruritusstimuli (Niemeier et al., 2000) als auch über alleinige Darbietung visueller (Lloyd et al., 2013; Lloyd et al., 2018; Lu et al., 2019; Papoiu et al., 2011b; Yu et al., 2017) oder auditiver Pruritusstimuli (Meeuwis et al., 2022; Mitchell, 1995; Swithenbank et al., 2016). Auf die unterschiedlichen Varianten der pruritogen-freien Pruritusstimulation wird im Folgenden eingegangen (siehe hierzu auch die Übersichtsarbeit von Schut et al., 2015a).

1.5.2.1 Audio-visuelle Pruritusstimulation

Erst selten wurde Pruritus mittels audio-visueller Stimuli induziert (Kamber et al., 2020; Niemeier et al., 2000). In der ersten Felduntersuchung nahm ein Publikum einer Fernsehshow an einem bildgestützten Vortrag zum Thema „Pruritus – was steckt dahinter?“ sowie an einem Vortrag, der das Ziel hatte Wohlbefinden und Entspannung zu induzieren, teil. Es wurde sowohl zur Baseline (t1) als auch nach beiden Vorträgen (t2: Pruritusvortrag; t3: Kontrollvortrag) zur Pruritusintensität befragt. Der Pruritus stieg von t1 zu t2 an und fiel zu t3 erwartungsgemäß ab. Ebenso zeigte sich ein signifikanter Anstieg in der Anzahl der Kratzbewegungen von t1 zu t2 (Niemeier et al., 2000). In der neueren Studie (Kamber et al., 2020) wurden Medizinstudierende ebenfalls vor und

nach Teilnahme an einer 45-minütigen Vorlesung zum Thema „Befall mit Parasiten“ zu ihrer Pruritusintensität befragt. Auch hier ergaben sich signifikante Anstiege in der Pruritusintensität durch die Teilnahme an der Vorlesung. Kratzverhalten wurde in dieser Studie nicht erfasst.

1.5.2.2 Visuelle Pruritusstimulation

Die Hypothese, dass sich Pruritus und Kratzverhalten auch allein durch die Präsentation von visuellem Stimulusmaterial induzieren lassen, konnte mittlerweile durch viele Studien bestätigt werden (Feneran et al., 2013; Holle et al., 2012; Kamber et al., 2020; Liljencrantz et al., 2017; Lloyd et al., 2013; Lloyd et al., 2018; Lu et al., 2019; Mochizuki et al., 2013; Najafi et al., 2020; Ogden & Zoukas, 2009; Papoiu et al., 2011b; Ward et al., 2013; Yu et al., 2017). In diesen Studien wurde einerseits statisches Bildmaterial von Pruritus bezogenen Stimuli zur Induktion von Pruritus und Kratzverhalten verwendet (Lloyd et al., 2013; Lloyd et al., 2018; Mochizuki et al., 2013), andererseits wurden Videos von sich kratzenden Individuen allein (Feneran et al., 2013; Holle et al., 2012; Lu et al., 2019; Najafi et al., 2020; Nakayama, 2004; Papoiu et al., 2011b; Ward et al., 2013; Yu et al., 2017) oder in Kombination mit Videos von sich bewegenden Kopfläusen (Ogden & Zoukas, 2009) genutzt, um Pruritus und/ oder Kratzverhalten zu induzieren. Weiterhin ist es möglich, durch das Beisammensein mit sich kratzenden Artgenossen Pruritus und Kratzverhalten zu erzeugen. Schon 1982 berichtete Pennebaker, dass Personen anfangen sich zu kratzen, wenn sie neben einer anderen, sich kratzenden Person sitzen (Pennebaker, 1982; zitiert nach Ogden & Zoukas, 2009). Das Phänomen des „ansteckenden Pruritus“ wurde mittlerweile nicht nur bei Menschen, sondern auch bei Affen (Feneran et al., 2013; Nakayama, 2004) und Mäusen (Liljencrantz et al., 2017; Yu et al., 2017) untersucht. Es zeigte sich, dass 87,5% der untersuchten Affen innerhalb von sechs Minuten Kratzverhalten zeigten, wenn sich zuvor ihr Käfigpartner gekratzt hatte. Hierbei fand rund die Hälfte der Kratzbewegungen innerhalb der ersten 60 Sekunden nach Beobachtung der Kratzbewegung statt (Feneran et al., 2013). In einer weiteren Studie imitierten Affen nur dann das Kratzverhalten ihres Käfignachbars, wenn dieser einen dritten sich kratzenden Affen beobachtete (Nakayama, 2004). Yu et al. (2017) zeigten weiterhin, dass Mäuse, in deren Nachbarkäfigen sich Artgenossen aufgrund von chronischem Pruritus häufig spontan kratzten, im Vergleich zu einer Kontrollgruppe, in deren

Nachbarkäfigen Mäuse kein exzessives Kratzverhalten aufwiesen, vermehrtes Kratzverhalten aufwiesen. In Replikations-Studien fand sich allerdings kein signifikant gehäuftes Kratzverhalten bei der Beobachtung sich kratzender Mäuse (Liljencrantz et al., 2017; Lu et al., 2019). Dies mag laut den Autoren zum einen daran liegen, dass in der Studie von Liljencrantz et al. (2017) die kratzenden Mäuse aufgrund von Histamin-Induktion Kratzverhalten zeigten, welches weniger exzessiv war als bei den Mäusen mit chronischem Juckreiz der erst genannten Studie (Yu et al., 2017). Außerdem wurden die Mäuse nicht wie in der Vorgängerstudie (Yu et al., 2017) in ihren Heimkäfigen beobachtet, sondern in Laborkäfigen, an die sie allerdings zunächst gewöhnt wurden (Liljencrantz et al., 2017). In einer weiteren Studie zu diesem Thema (Lu et al., 2019) beobachteten die Mäuse andere sich kratzende Mäuse über ein Tablet. Auch in dieser Studie war bei den kratzenden Mäusen, die als Pruritusstimuli dienten, das Kratzverhalten mittels Histamin-Applikation erzeugt worden (Lu et al., 2019). Dass Pruritus mittels visueller Stimuli induzierbar ist, konnte somit sowohl im Human- als auch im Tierbereich gezeigt werden. Weitgehend unerforscht blieb bislang allerdings die neuronale Grundlage visuell induzierten Pruritus bei Patienten mit chronischem Pruritus. Die Untersuchung der zentralnervösen Verarbeitung visuell induzierten Pruritus bei ND-Patienten war daher das Ziel einer Studie, die in diese Habilitationsschrift einging.

1.5.2.3 Auditive Pruritusstimulation

In einem weiteren Ansatz ist es zudem gelungen, Pruritus allein über die Präsentation von Kratzgeräuschen zu induzieren (Meeuwis et al., 2022; Swithenbank et al., 2016). Die Präsentation von Kratzgeräuschen führte sowohl bei PS-Patienten als auch bei hautgesunden Kontrollen zu signifikant intensiverem Pruritus als die Präsentation von Geräuschen des Hautreibens. Hierbei machte es keinen Unterschied, ob die Geräusche auf einem menschlichen Körperteil oder auf nicht-menschlicher Haut hervorgerufen wurden. Allerdings stellte die Frequenz, mit der die Geräusche präsentiert wurden, eine wichtige Moderatorvariable dar: Je höher die Frequenz war, desto größer war auch der wahrgenommene Pruritus (Swithenbank et al., 2016). In einer aktuellen Studie (Meeuwis et al., 2022) ließ sich das Ergebnis, dass Pruritus bei hautgesunden Personen über Geräusche induziert werden kann, replizieren.

Allerdings führten in dieser Studie Geräusche des Hautreibens und Kratzens beide zu einer signifikanten Steigerung des Pruritus.

1.5.2.4 Vor- und Nachteile der pruritogen-freien Methode der Pruritusinduktion

Nachdem im vorherigen Abschnitt pruritogen-freie Methoden der Pruritusinduktion vorgestellt wurden, werden nun die Vor- und Nachteile dieses Ansatzes im Vergleich zu pruritogen-gebundenen Methoden der Pruritusinduktion zusammengefasst. Diese werden teilweise auch von van Laarhoven et al. (2020) in ihrem Kommentar zu einem der Artikel, der in diese Habilitationsschrift einging (Marzell et al., 2020), genannt. Die Methode der (audio-)visuellen Pruritusinduktion hat den großen Vorteil, dass bei ihrer Verwendung keine Hautmanipulation notwendig ist und somit davon auszugehen ist, dass bei ihrer Anwendung weniger psychisches Unwohlsein auftritt als bei der Applikation einer pruritogenen Substanz auf der Haut. Die Verwendung der Histamin-Iontophorese wurde in einer Studie sogar als Methode der Akutstressinduktion verwendet (Tran et al., 2010). Dies ist insofern bedeutsam, als emotionale Belastung, beispielsweise in Form von Angst, Pruritus verstärken kann (Sanders & Akiyama, 2018) und somit der Anteil der Pruritusintensität, der auf das durch die Hautmanipulation induzierte Unwohlsein zurückgeht, nicht mehr von dem zu trennen ist, der durch die Applikation des Pruritogens zustande kommt. Die pruritogen-freie Pruritusinduktion bringt weiterhin den großen Vorteil mit sich, dass das, was die Probanden während (audio-)visueller Pruritusinduktion erfahren, sehr eng mit dem verwandt ist, was Patienten mit Hauterkrankungen in ihrem Alltag erleben: Der Juckreiz ist nicht auf eine Körperregion begrenzt und entsteht „spontan“, ohne direkte physische Manipulation, wodurch er ggf. auch als weniger kontrollierbar und vorhersagbar erlebt wird als der durch Pruritogene erzeugte Pruritus. Die möglicherweise geringere wahrgenommene Kontrolle und Vorhersagbarkeit lässt somit den pruritogen-frei induzierten Pruritus alltagsnäher erscheinen als den mittels Pruritogen induzierten Pruritus. Bislang war allerdings unbekannt, ob sich die beiden methodischen Zugänge auch hinsichtlich der Intensität und Qualität des durch sie ausgelösten Pruritus unterscheiden. Ebenfalls bislang unklar blieb, welche Hirnregionen bei Pruritispatienten durch pruritogen-freie Pruritusinduktion stimuliert werden. Die Beantwortung dieser Fragen ist wesentlich für das Verständnis von Forschungsergebnissen zu psychologischen Moderatoren von pruritogenfrei

induziertem Pruritus. Entsprechend widmen sich die ersten Studien, die in diese Habilitationsschrift einfließen, diesen Fragen.

1.6 Zusammenfassung des Forschungsstands und Ziele dieser Arbeit

Bei Pruritus handelt es sich um ein sehr häufiges Symptom der Allgemeinbevölkerung (Dalgard et al., 2004a, b) und ein noch sehr viel häufigeres Symptom bei Patienten mit verschiedenen Hauterkrankungen (Schut et al., 2019).

Zur Induktion von Pruritus im Labor sind unterschiedliche Methoden verfügbar. Allerdings profitiert die Methode der pruritogen-freien Pruritusinduktion durch ihre hohe Vergleichbarkeit mit dem, was Patienten mit chronischem Pruritus im Alltag erleben, und davon, dass bei dieser Methode die Pruritusinduktion nicht mit einer Hautmanipulation und dem ggf. damit verbundenen Unwohlsein konfundiert ist. Bislang blieb allerdings unklar, ob Pruritus, der über diese Methode induziert wird, mit durch Pruritogene erzeugten Pruritus hinsichtlich seiner Intensität, Qualität und Lokalisation vergleichbar ist. Zudem wurde die neuronale Grundlage von (audio-) visuell induziertem Pruritus nur sehr spärlich, nämlich erst einmal bei hautgesunden Probanden (Holle et al., 2012) und einmal bei PS-Patienten (Najafi et al., 2020), bei welchen Juckreiz zwar häufig vorkommt (Baughman & Sobel, 1971; Komiya et al., 2020; Reszke et al., 2019), aber nicht als Kardinalsymptom gilt, im Vergleich zu hautgesunden Kontrollen untersucht. Informationen hierzu sind notwendig, um Wissenschaftlerinnen und Wissenschaftlern zukünftiger Studien die Auswahl der geeigneten Methode für ihre Fragestellung zu erleichtern.

Das biopsychosoziale Modell des chronischen Pruritus (Verhoeven et al., 2007) geht davon aus, dass unterschiedliche biopsychosoziale Faktoren Pruritus verstärken oder reduzieren. In Vorgängerstudien (Bartels et al., 2018; Bartels et al., 2017a; Bartels et al., 2017b; Gupta et al., 1988; Gupta et al., 1994; Holle et al., 2012; Najafi et al., 2020; Silverberg et al., 2019; Silverberg et al., 2020; van Laarhoven et al., 2010; van Laarhoven et al., 2011; van Laarhoven et al., 2012; Verhoeven et al., 2006; Weiss et al., 2016) wurden zwar bereits Zusammenhänge zwischen Persönlichkeitsfaktoren, Selbstaufmerksamkeit, Angst, Depression und der Erwartungshaltung und Pruritus untersucht, allerdings nur selten für experimentell induzierten Pruritus und hier zumeist bei hautgesunden Personen und nicht bei Patienten mit chronischem Pruritus. Um die

Therapie des als sehr unangenehm empfundenen Symptoms Pruritus (Reich et al., 2016; Yosipovitch et al., 2002) zu verbessern und dadurch das Wohlbefinden von Patienten mit chronischem Pruritus zu steigern, ist es essentiell psychologische Faktoren als Moderatoren von experimentell induziertem Pruritus zu untersuchen.

Die nachfolgende Darstellung der hier zusammengefassten Studien fokussiert auf diese zentralen Fragestellungen und sieht zugunsten der Übersichtlichkeit von einer Darstellung aller Ergebnisse der Studien ab. Die interessierte Leserschaft sei auf die angehängten Artikel verwiesen, in welchen weitere Ergebnisse der Studien zu finden sind.

2. Zusammenfassung der durchgeführten Studien

Im nun folgenden Teil der Habilitationsschrift werden zunächst die Studien zur Validierung der pruritogen-freien Methode der Pruritusinduktion vorgestellt. Hierbei wird zu Beginn auf die Untersuchung der Vergleichbarkeit von pruritogen-frei induziertem Pruritus im Vergleich zu Histamin-induziertem Pruritus bezüglich Intensität, Qualität und Lokalisation des Pruritus eingegangen. Anschließend geht es um die zentralnervöse Verarbeitung von pruritogen-frei induziertem Pruritus bei ND-Patienten. Dann werden die wichtigsten Ergebnisse der Studien erläutert, in denen Persönlichkeitsfaktoren, Selbstaufmerksamkeit, Angst und Depression sowie die Erwartungshaltung als Moderatoren für pruritogen-frei erzeugten Pruritus und Kratzverhalten untersucht wurden. Der nachfolgende Kasten fasst die zentralen Inhalte der Studien zusammen:

(1) Validierung einer pruritogen-freien Methode der Pruritusinduktion

a) *Untersuchung der Nicht-Unterlegenheit von pruritogen-frei induziertem Pruritus im Vergleich zu pruritogen-induziertem Pruritus hinsichtlich seiner Intensität*

b) *Untersuchung der Qualität und Lokalisation von pruritogen-frei und pruritogen-induziertem Pruritus*

c) *Untersuchung zentralnervöser Verarbeitung von pruritogen-frei induziertem Pruritus bei Patienten mit chronischem Pruritus*

(2) Untersuchung, ob folgende psychologische Faktoren Moderatoren für die Reagibilität auf audio-visuelle Pruritusstimuli darstellen

a) *Persönlichkeitsfaktoren*

b) *Selbstaufmerksamkeit*

c) *Angst/ Depression*

d) *Erwartungshaltung*

2.1 Validierung einer pruritogen-freien Methode der Pruritusinduktion

Die ersten Studien der kumulativen Habilitationsschrift widmen sich der Validierung der Methode der Pruritusinduktion mittels (audio-)visueller Stimuli. Die unter 2.1.1 dargestellten Studien beantworten die Frage, ob und unter welcher Bedingung die Präsentation audio-visueller Pruritusstimuli eine Alternative zu der Pruritusinduktion mittels Histamin-Iontophorese darstellt. In der unter 2.1.2 dargestellten Studie wurde die zentralnervöse Verarbeitung audio-visueller Pruritusstimuli bei Patienten mit chronischem Pruritus untersucht.

2.1.1 Audio-visuelle Pruritusstimuli als Alternative zur Histamin-Iontophorese

Marzell R, Kupfer J, Reichwein G, Gieler U, ***Schut C*****. Itch induction by audiovisual stimuli and histamine iontophoresis: a randomized, controlled non-inferiority study. British Journal of Dermatology 2020;182:1253-1261 (IF 2022: 11.113)*

Es wurden zwei randomisierte kontrollierte Studien durchgeführt, deren Ziel es war zu prüfen, ob eine pruritogen-freie Pruritusstimulation im Ergebnis einer Histamin-induzierten ebenbürtig ist. Im Fall dessen, dass beide Pruritusinduktions-Methoden vergleichbar intensiven Pruritus hervorrufen, würde die Präsentation audio-visueller Pruritusstimuli in zukünftigen Studien eine gute Alternative zur Pruritusinduktion mittels Histamin-Iontophorese darstellen, da sie keine direkte Hautmanipulation erfordert.

Beide Studien waren methodisch als randomisierte kontrollierte Nicht-Unterlegenheitsstudien angelegt und verglichen die durch Histamin-Iontophorese ausgelösten Effekte mit denen einer audio-visuellen Stimulation. Zum Zeitpunkt der Datenerhebung vorliegende Daten (Schut et al., 2014; Schut et al., 2015b) ließen die Hypothese zu, dass der Pruritusanstieg höher ausfällt, wenn vor der Präsentation der audio-visuellen Pruritusstimuli ein Priming in Form eines bildgestützten Vortrags erfolgt, der die Aufmerksamkeit auf die Haut lenkt. Studie 2 unterschied sich daher in diesem Aspekt von Studie 1, verwendete aber ansonsten dieselbe Methodik.

Sowohl die Histamin-Iontophorese als auch die Präsentation der audio-visuellen Pruritusstimuli führte in beiden Studien zu einem signifikanten Anstieg in der Pruritusintensität (alle $p<0.05$). Hinsichtlich des Kratzverhaltens ergaben sich signifikante Anstiege in der Anzahl der Kratzbewegungen (alle $p<0.05$) sowie tendenziell signifikante Anstiege in der Kratzdauer (alle $p<0.07$).

Die Nicht-Unterlegenheits-Tests ergaben in Studie 1 (kein Priming) eine Unterlegenheit von audio-visuell induziertem im Vergleich zu Histamin-induziertem Pruritus: Sowohl der mittels audio-visueller Stimuli maximal induzierte Pruritus als auch der mittels audio-visueller Stimuli induzierte Pruritus, der unmittelbar im Anschluss an die Pruritusinduktions-Phase gemessen wurde, waren geringer als der mittels Histamin-Iontophorese induzierte Pruritus.
In Studie 2 (Priming) konnte eine Nicht-Unterlegenheit des durch audio-visuelle Stimuli maximal induzierten Pruritus gezeigt werden. Hingegen trat auch hier eine Unterlegenheit bezüglich des induzierten Pruritus auf, der unmittelbar im Anschluss an die Pruritusinduktions-Phase gemessen wurde. Die grafische Darstellung der Ergebnisse der Nicht-Unterlegenheits-Tests findet sich in Abbildung 2.

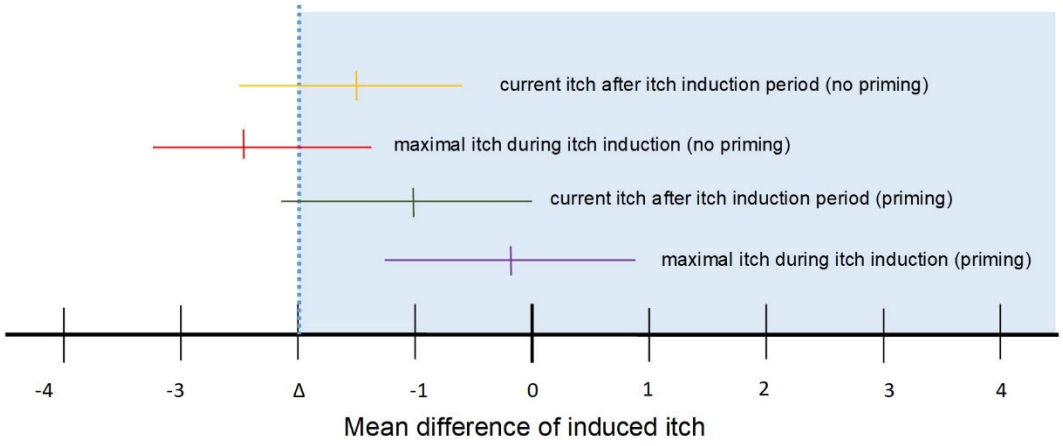

Abbildung 2. Ergebnisse der Nicht-Unterlegenheitstests (Abbildung aus Marzell et al., 2020). Dargestellt sind die Mittelwertdifferenzen und 90%-Konfidenzintervalle für induzierten Pruritus. Befindet sich die Untergrenze des 90%-Konfidenzintervalls innerhalb des hellblau markierten Bereichs liegt eine Nicht-Unterlegenheit von audio-visuell induziertem Pruritus im Vergleich zu Histamin-induziertem Pruritus vor. Eine Nicht-Unterlegenheit konnte für maximal induzierten Pruritus nach attentionaler Fokussierung (Priming (lila)), jedoch nicht für maximal induzierten Pruritus ohne vorherige attentionale Fokussierung auf die Haut (kein Priming, rot) und auch nicht für induzierten Pruritus, gemessen unmittelbar nach der Pruritusinduktions-Phase (grün und gelb), gezeigt werden.

Der Vergleich bezüglich der Lokalisation und Qualität von audio-visuell induziertem Pruritus und Histamin-induziertem Pruritus (nach Priming) ergab, dass sich Histamin-induzierter Pruritus auf die Stelle, an der Histamin appliziert wurde, beschränkte, während die Präsentation audio-visueller Pruritusstimuli zu Pruritus an verschiedenen Körperstellen führte. Histamin-induzierter Pruritus entstand signifikant häufiger am Arm als audio-visuell induzierter Pruritus. Hingegen begann audio-visuell induzierter Pruritus signifikant häufiger im Gesicht oder am Rücken als Histamin-induzierter Pruritus. Typische Pruritusorte nach audio-visueller Pruritusinduktion waren zudem der Kopf, der Rücken, die Hände, die Beine und die Füße (siehe Abbildung 3). Bezüglich der Qualität ergab sich, dass Histamin-induzierter Pruritus als stärker beißend, schmerzhaft, brennend, oberflächlich lokalisiert und stechend empfunden wurde als audio-visuell induzierter Pruritus.

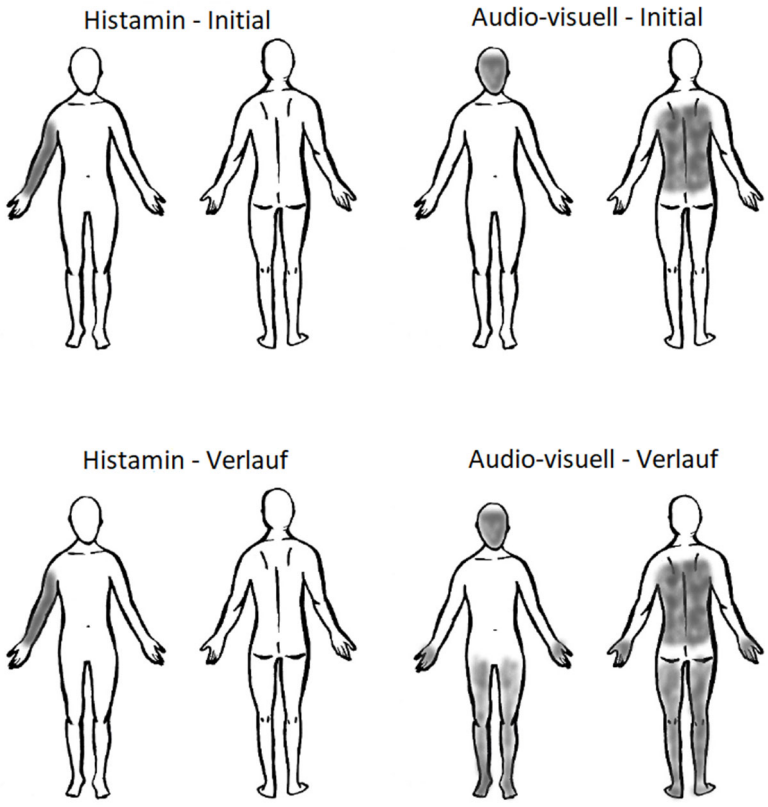

Abbildung 3. Lokalisation von audio-visuell und Histamin-induziertem Pruritus. Grau markiert sind Körperstellen, an denen signifikant mehr Personen der einen Gruppe im Vergleich zur anderen Gruppe Pruritus initial oder im Verlauf empfanden. Histamin: Personen mit Histamin-induziertem Pruritus; Audio-visuell: Personen mit audio-visuell induziertem Pruritus.

Zusammenfassend zeigen die beiden Studien, dass die Intensität des audio-visuell induzierten Pruritus nur dann mit der des Histamin-induzierten Pruritus vergleichbar ist, wenn er durch Priming intensiviert wird. Die nach der Induktionsphase gemessenen Intensitätswerte weisen außerdem darauf hin, dass diese Vergleichbarkeit auf die Induktionsphase beschränkt bleibt. Zugleich bestätigen die Studiendaten die Annahme, dass audio-visuell induzierter Pruritus stärker über den gesamten Körper verteilt ist und auch hinsichtlich der Qualität möglicherweise alltäglichem Pruritus ähnlicher ist.

2.1.2 Zentralnervöse Verarbeitung pruritogen-frei induzierten Pruritus

Schut C, *Mochizuki H, Grossman SK, Lin AC, Conklin CJ, Mohamed FB, Gieler U, Kupfer J, Yosipovitch G. Brain processing of contagious itch in patients with atopic dermatitis. Front Psychol 2017 Jul 25; 8: 1267. doi: 10.3389/fpsyg.2017.01267 (IF 2022: 4.232)*

Zum Zeitpunkt dieser Untersuchung lagen nur Studienergebnisse zur zentral nervösen Verarbeitung von visuell induziertem Pruritus bei hautgesunden Personen vor (Holle et al., 2012; Mochizuki et al., 2013). Diese zeigten, dass visuell induzierter Pruritus zu einer Aktivierung ähnlicher Gehirnareale führt wie die Applikation von Pruritogenen (Darsow et al., 2000; Herde et al., 2007; Ishiuji et al., 2009; Leknes et al., 2007; Mochizuki et al., 2007; Schneider et al., 2008; Valet et al., 2008). Unklar blieb bis dahin allerdings, ob die Präsentation visueller Pruritusstimuli auch bei ND-Patienten entsprechende Effekte hervorruft. Diese Studie war als randomisierte, kontrollierte Studie angelegt und wurde im Rahmen eines von der DFG geförderten Forschungsaufenthalts in den USA durchgeführt. Geplant war die Untersuchung der Effekte von Stressbewältigung auf induzierten Pruritus und auf die Aktivität in mit Pruritus assoziierten Gehirnarealen bei ND-Patienten im Vergleich zu hautgesunden Kontrollen (DFG-Projektnummer: 251171139). Aufgrund von Schwierigkeiten bei der Probandenrekrutierung wurden allerdings nur die Daten zur zentralnervösen Verarbeitung von visuell induziertem Pruritus bei ND-Patienten publiziert.

Es wurden n=11 ND-Patienten eingeschlossen, welche zum Zeitpunkt der Datenerhebung Pruritus der Stärke ≥ 4 (Visuelle Analogskala (VAS) 0-10) und eine Reagibilität auf visuelle Pruritusstimuli aufwiesen. Alle Probanden durchliefen zwei

Untersuchungsphasen, wovon die erste innerhalb des MRT stattfand und die zweite außerhalb. Beide Untersuchungsphasen waren insofern gleich, als den Probanden zwei Videos, ein Pruritus induzierendes EV und ein nicht Pruritus-induzierendes KV, präsentiert wurden. Das Kratzverhalten wurde nur außerhalb des Scanners per Videokamera aufgezeichnet. Pruritus wurde sowohl im als auch außerhalb des Scanners gemessen. Während beider Untersuchungsphasen kam es zu einem signifikanten Anstieg in der Pruritusintensität durch die Präsentation des EVs (alle $p<0.05$). Außerhalb des Scanners ergab sich ebenso ein signifikanter Anstieg in der Anzahl der Kratzbewegungen und Kratzdauer durch das EV ($p<0.05$). Die Pruritusintensität und das Kratzverhalten während der Präsentation des KVs und EVs sind in Abbildung 4 dargestellt.

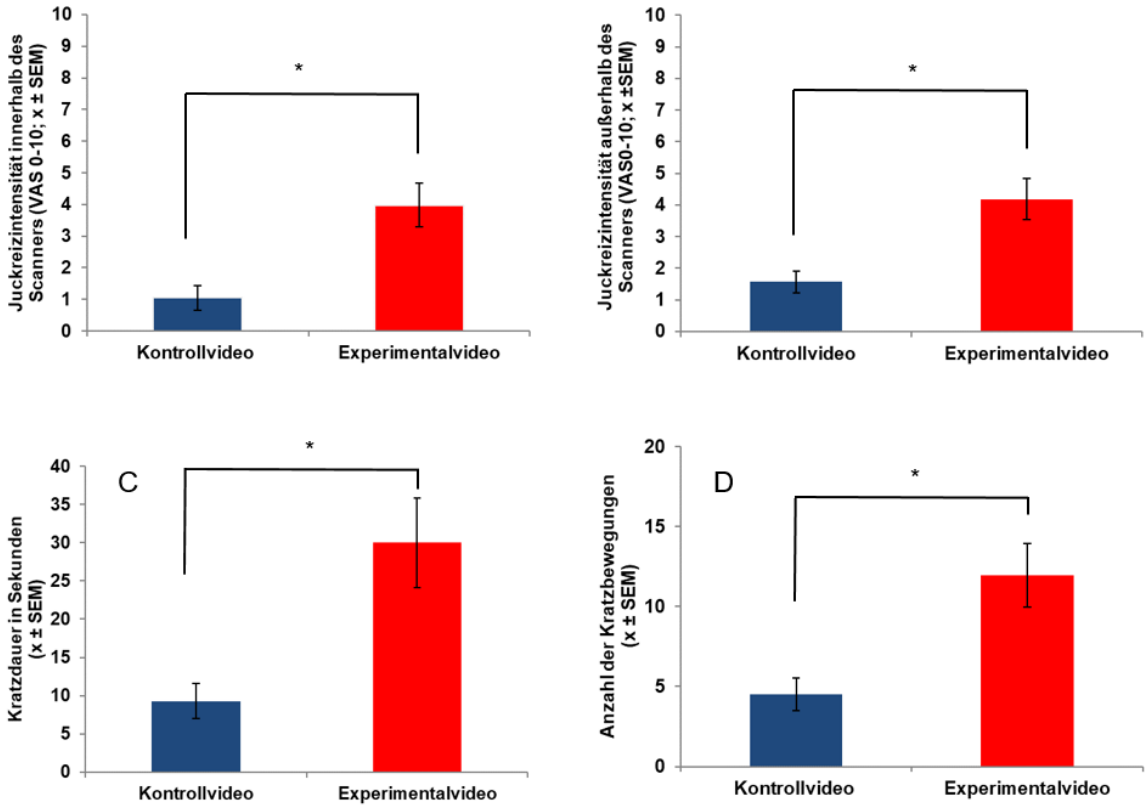

Abbildung 4. Pruritusintensität und Kratzverhalten während der Experimental- und Kontrollbedingung (Abbildung modifiziert nach Schut et al., 2017). Während des EVs zeigte sich im Vergleich zum KV eine Zunahme in der Pruritusintensität innerhalb (A) und außerhalb des Scanners (B) sowie eine Zunahme in der Anzahl der Kratzbewegungen (C) und der Kratzdauer (D) außerhalb des Scanners. Dargestellt sind Mittelwerte (x) und Standardfehler (SEM). Die Mittelwertunterschiede sind auf dem 0.05 Signifikanzniveau signifikant.

Bezüglich der zentralnervösen Verarbeitung der visuellen Pruritusstimuli zeigte sich während der Präsentation visueller Pruritusstimuli im Vergleich zur Kontrollbedingung eine vermehrte Aktivierung des SMA, des rechten OFC und des linken ventralen Striatums (unkorrigiertes $p < 0.001$; Cluster-Größe (k)>50; siehe Abbildung 5). Zudem ergab sich ein tendenziell signifikanter Zusammenhang zwischen dem durchschnittlichen Anstieg in der Pruritusintensität und der Zunahme in der Aktivierung des (Prä-)cuneus, des rechten temporalen Kortex und des rechten opercularen Kortex (unkorrigiertes $p>0.005$; $k>50$).

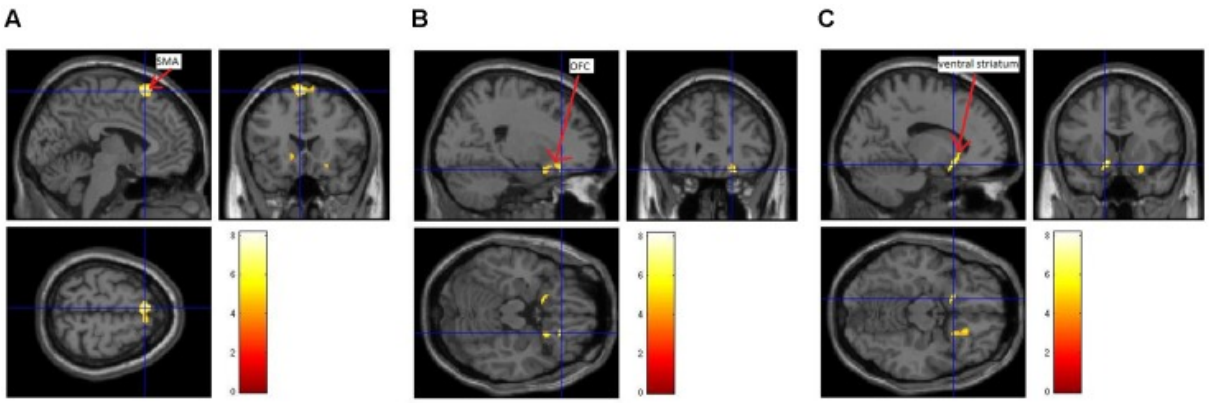

Abbildung 5. Pruritusbedingte Gehirnaktivität (Abbildung aus Schut et al., 2017). Während der Präsentation des EVs zeigte sich im Vergleich zur Präsentation des KVs eine Zunahme in der Aktivierung des SMA (A), des rechten OFC (B) und des linken ventralen Striatums (C).

Zusammenfassend liefert diese Studie erste Hinweise darauf, dass visuell induzierter Pruritus bei Patienten mit chronischem Pruritus zu einer Aktivierung des frontostriatalen Netzwerks führt. Dieses war in einer Vorgängerstudie bei hautgesunden Probanden nach visueller Pruritusinduktion nicht aktiviert (Holle et al., 2012). Teile dieses Netzwerks, der SMA und die Basalganglien, zeigten sich aber bereits bei Patienten mit chronischem Pruritus im Vergleich zu hautgesunden Kontrollprobanden während Pruritus/ Kratzen überaktiviert (Ishiuji et al., 2009; Mochizuki et al., 2015; Schneider et al., 2008). Sie scheinen somit besonders bei Patienten mit chronischem Pruritus an der Verarbeitung Pruritus stimulierender Reize beteiligt zu sein.

2.2 Moderatoren der Reagibilität auf audio-visuelle Pruritusstimuli

2.2.1 Persönlichkeit, Selbstaufmerksamkeit, Angst und Depression

Schut C**+******, Bosbach S*, Gieler U, Kupfer J. Personality traits, depression and itch in patients with atopic dermatitis in an experimental setting: a regression analysis. Acta Dermato Venereologica 2014; 94: 20-25. (IF 2022: 3.875)**

Schut C**+******, Muhl S*, Reinisch K, Claßen A, Jäger R, Gieler U, Kupfer J. Agreeableness and self-consciousness as predictors of induced scratching and itch in patients with PS. International Journal of Behavioral Medicine. 2015b; 22: 726-734. (IF 2022: 2.5)**

Schut C**+******, Reinisch K*, Classen A, Andres S, Gieler U, Kupfer J. Agreeableness as Predictor of Induced Scratching in Patients with Atopic Dermatitis: A Replication Study. Acta Dermato Venereologica 2018; 98: 32-37. (IF 2022: 3.875)**

*+ korrespondierende Autorin; * geteilte Erstautorenschaft*

Ziel dieser Studien war es, psychologische Moderatoren des audio-visuell induzierten Pruritus und des damit verbundenen Kratzverhaltens zu identifizieren. Konkret wurde geprüft, ob die fünf großen Persönlichkeitsfaktoren (sog. Big Five (Borkenau & Ostendorf, 2008)), Selbstaufmerksamkeit, eine vermehrte dispositionelle Angst oder eine erhöhte Ausprägung von Anzeichen einer Depression die Pruritusreagibilität bei Patienten mit chronischem Pruritus moderieren.

Zur Untersuchung kamen Patienten mit ND (Schut et al., 2014; Schut et al., 2018) und mit PS (Schut et al., 2015b). Zum Vergleich wurden jeweils auch die Daten hautgesunder Kontrollen herangezogen. Dabei bedienten sich zwei Studien (Schut et al., 2018; Schut et al., 2015b) aus demselben Pool hautgesunder Probanden und zogen jeweils die heran, die eine möglichst hohe Übereinstimmung hinsichtlich Alter und Geschlecht mit den Patienten aufwiesen. Dies führte dazu, dass einige Daten doppelt verwertet wurden.

Die Präsentation des EVs führte in allen Studien zu einem signifikanten Anstieg in der Pruritusintensität und teilweise auch des Kratzverhaltens (Schut et al., 2014; Schut et al., 2018; Schut et al., 2015b).

Das Ausmaß des induzierten Pruritus konnte bei ND-Patienten regressionsanalytisch über die Depressionswerte vorhergesagt werden (Schut et al., 2014). Die Ausprägung der Depression erklärte 17,5% der Varianz des induzierten Pruritus. In einer weiteren Studie konnte bei PS-Patienten öffentliche Selbstaufmerksamkeit als Moderator von induziertem Pruritus identifiziert werden und sagte knapp 29% der Varianz vorher (Schut et al., 2015b). Die Korrelation war positiv. In der dritten Studie (Schut et al., 2018) mit ND-Patienten gelang es allerdings nicht, diese Zusammenhänge zu replizieren ($p > 0.05$; $r \leq 0.112$).

Dagegen ergaben sich sowohl in dieser Studie (Schut et al., 2018) als auch in den beiden anderen (Schut et al., 2014; Schut et al., 2015b) signifikant negative Zusammenhänge zwischen pruritogen-frei induziertem Kratzverhalten und dem Persönlichkeitsfaktor Verträglichkeit. In der zuerst durchgeführten Studie (Schut et al., 2014) klärte dieser Persönlichkeitsfaktor zusammen mit öffentlicher Selbstaufmerksamkeit mehr als 53% der Varianz des Kratzverhaltens der ND-Patienten auf. Öffentliche Selbstaufmerksamkeit war signifikant positiv mit induziertem Kratzverhalten assoziiert. In den beiden folgenden Studien (Schut et al., 2018; Schut et al., 2015b) ließen sich regressionsanalytisch bei den Patienten allein durch Verträglichkeit zwischen 16% und 38% (nach Ausschluss eines Ausreißerwertes) der Varianz des induzierten Kratzverhaltens erklären.

Zusammenfassend zeigten die Studien also, dass es sich bei Verträglichkeit um einen robusten Prädiktor von audio-visuell induziertem Kratzverhalten bei Patienten mit chronischem Pruritus handelt. Hinsichtlich des induzierten Pruritus als solchen sind die Zusammenhänge weniger eindeutig. Während sich in zwei Studien (Schut et al., 2014; Schut et al., 2015b) das Ausmaß induzierten Pruritus teilweise über Depression bzw. öffentliche Selbstaufmerksamkeit vorhersagen ließ, stellten diese Faktoren in der dritten Studie (Schut et al., 2018) keine signifikanten Prädiktoren für induzierten Pruritus dar.

Des Weiteren zeigte sich, dass der pruritogen-frei induzierte Pruritus und das Kratzverhalten bei Hautgesunden mit keinem der genannten Merkmale in bedeutsamem Zusammenhang zu stehen scheint. Auch wenn sich in einer Studie signifikant positive Zusammenhänge zwischen privater Selbstaufmerksamkeit und

induziertem Pruritus (Schut et al., 2018) ergaben, sprechen die sonstigen Befunde eher dagegen, dass Persönlichkeitseigenschaften, Angst oder Depression das pruritogen-frei induzierte Pruritusgeschehen bei Hautgesunden moderieren.

2.2.2 Erwartungshaltung

Schut C*[+]*, *Rädel A, Frey L, Gieler U, Kupfer J. Role of personality and expectations for itch and scratching induced by audiovisual stimuli. European Journal of Pain 2016; 20:14-18. doi: 10.1002/ejp.751 (IF 2022: 3.651)*

+ korrespondierende Autorin;

Bisherige Studien lieferten die Erkenntnis, dass Nocebo-Effekte für klinisch und experimentell bedingten Pruritus relevant sind (Bartels et al., 2014; van Laarhoven et al., 2011; van Laarhoven et al., 2015). Es gibt allerdings nur sehr wenige Studien, die die Effekte unterschiedlicher Vorabinformationen zu Pruritus bei Patienten mit klinisch bedingtem Pruritus im experimentellen Setting untersuchten (Hermanns & Scholz, 1992; Napadow et al., 2015; Scholz & Hermanns, 1994). Ob sich Effekte unterschiedlicher Informationen bei Patienten mit chronischem Pruritus und hautgesunden Kontrollprobanden auch dann zeigen, wenn Pruritus/ Kratzverhalten mittels audio-visueller Pruritusstimuli induziert werden, war bislang gänzlich unklar. Die Untersuchung der Effekte von Vorinformationen zu Pruritusstimuli war deshalb das Ziel der Studie.

Die Studie war als randomisierte, kontrollierte Studie angelegt. Es wurden 120 Probanden (60 ND-Patienten und 60 Hautgesunde) randomisiert einer von drei Gruppen zugewiesen. Sie erhielten zu Beginn der Untersuchung entweder keine, realistische oder katastrophisierende Informationen zu später präsentierten audio-visuellen Pruritusstimuli. Die Pruritusintensität wurde messwiederholt, also unmittelbar nach der Präsentation des KV als auch nach der Präsentation des Pruritus erzeugenden EV erfasst. Die Videos wurden gegenbalanciert dargeboten. Zudem wurde das Kratzverhalten der Studienteilnehmer während der Präsentation der audio-visuellen Stimuli aufgezeichnet.

Das EV führte unabhängig von der Vorinformation zu intensiverem Pruritus und mehr Kratzbewegungen als das KV, sowohl bei ND-Patienten als auch bei den hautgesunden Kontrollprobanden (alle $p<0.05$). Deskriptiv ergab sich auch ein Anstieg der Kratzdauer, der allerdings nicht signifikant wurde. Die Ergebnisse sind in Abbildung 6 dargestellt.

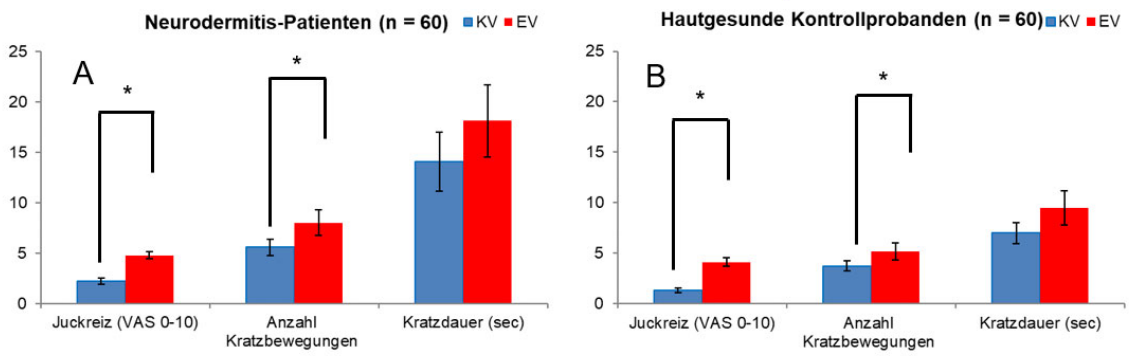

Abbildung 6. Effekte der Präsentation des EVs im Vergleich zum KV auf Pruritus und Kratzverhalten. Bei ND-Patienten (A) und hautgesunden Kontrollen (B) ergaben sich signifikante Effekte auf den Pruritus und die Anzahl der Kratzbewegungen durch das EV (alle p-Werte < 0.05; mit * gekennzeichnet), nicht aber auf die Kratzdauer (alle p-Werte > 0.05). Dargestellt sind x ± SEM.

Es ergaben sich keine signifikanten Effekte durch die Vorinformation auf das Ausmaß des induzierten Pruritus (alle $p > 0.05$; siehe Abbildung 7).

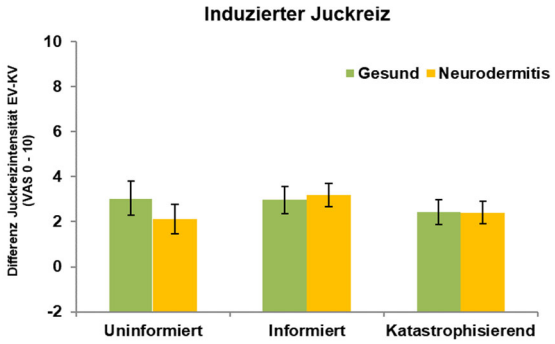

Abbildung 7. Effekte der Vorinformation auf induzierten Pruritus. Es ergaben sich keine signifikanten Effekte (alle p-Werte > 0.05). Dargestellt sind x ± SEM.

Effekte auf das Kratzverhalten ergaben sich nur in der Gruppe der ND-Patienten. Hier zeigte sich, dass Patienten, die vorab eine realistische Information bezüglich der Pruritusstimuli erhalten hatten, einen signifikant geringeren Anstieg in der *Anzahl der Kratzbewegungen und eine geringere Kratzdauer* aufwiesen als uninformierte ND-Patienten ($p<0.05$). Die Ergebnisse sind in Abbildung 8 dargestellt.

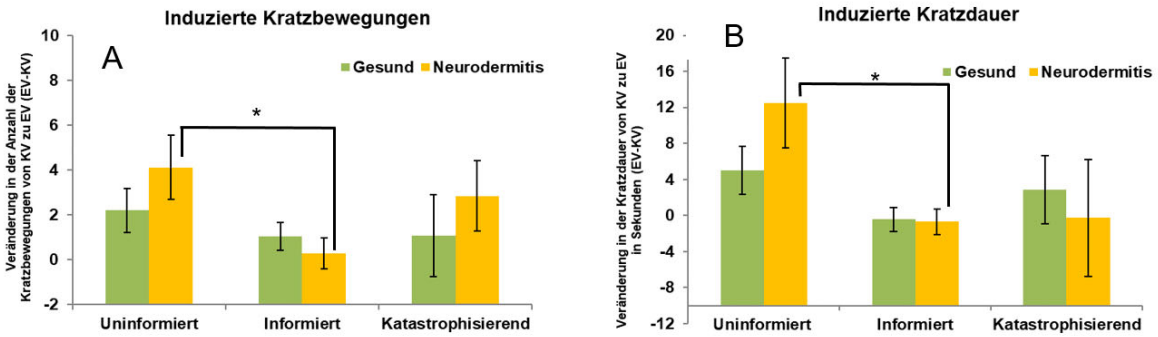

Abbildung 8. Effekte der Vorinformation auf induzierte Kratzbewegungen sowie induzierte Kratzdauer. Es ergaben sich signifikante Gruppenunterschiede zwischen informierten und uninformierten ND-Patienten hinsichtlich der induzierten Kratzbewegungen (A) und der induzierten Kratzdauer (B; beide $p < 0.05$). Dargestellt sind $x \pm SEM$.

Zusammenfassend zeigten sich Erwartungs-Effekte, induziert über unterschiedliche Vorinformationen zu Pruritusstimuli, also nur auf Kratzverhalten, nicht aber auf Pruritus und nur in der Gruppe der ND-Patienten. Diese Ergebnisse sind wichtig, da sie nahelegen, dass eine realistische Aufklärung zu auftretenden Symptomen der zugrundeliegenden Hauterkrankung notwendig ist, um Kratzverhalten im Alltag zu reduzieren. Ein Nicht-Ansprechen der Symptome scheint demnach nicht zielführend. Dies sollte bei der Aufklärung dermatologischer Patienten zukünftig berücksichtigt werden.

3. Diskussion und Ausblick

3.1 Zusammenfassung und Interpretation der Ergebnisse

3.1.1 Validierung der pruritogen-freien Methode der Pruritusinduktion

Ziel der vorliegenden Arbeiten war es, die Methode der pruritogen-freien Pruritusinduktion zu validieren. Es zeigte sich, dass audio-visuell induzierter Pruritus hinsichtlich seiner maximalen Intensität in den Induktionsphasen mit Histamin-induziertem Pruritus vergleichbar ist und eine andere Qualität aufweist als Histamin-induzierter Pruritus. Audio-visuell induzierter Pruritus wird als weniger beißend, schmerzhaft, brennend, oberflächlich lokalisiert und stechend empfunden als durch Histamin-Iontophorese induzierter Pruritus (Marzell et al., 2020). Wenn es also darum geht, möglichst realitätsnahen, reinen, wenig schmerzhaften Pruritus zu induzieren, ist die Methode der audio-visuellen Pruritusinduktion offensichtlich pruritogen-gebundenen Methoden vorzuziehen. Darüber hinaus betrifft audio-visuell induzierter Pruritus mehrere Körperareale als Histamin-induzierter Pruritus und breitet sich im Verlauf der Untersuchung vom Kopf und Rumpf in Richtung Beine und Hände aus, während Histamin-induzierter Pruritus auf die Stelle der Applikation begrenzt bleibt (Marzell et al., 2020). Dieses Verteilungsmuster passt zu Ergebnissen anderer Studien, in denen audio-visuell induzierter Pruritus ebenfalls zu generalisiertem Pruritus bzw. Kratzverhalten führte (Papoiu et al., 2011b; Ward et al., 2013; Kamber et al., 2020).

Des Weiteren zeigte sich, dass die Methode der pruritogen-freien Pruritusinduktion zentralnervöse Effekte hat, die auch bei Anwendung pruritogen-gebundener Pruritusinduktionsmethoden zu beobachten sind (Hsieh et al., 1994; Ishiuji et al., 2009; Mochizuki et al., 2015; Schneider et al., 2008). Sowohl der SMA, OFC als auch das Striatum zeigten sich bei Patienten mit chronischem Pruritus während visuell induziertem Pruritus aktiviert. Diese Gehirnregionen gehören zum fronto-striatalen Netzwerk, welches eine wichtige Rolle für Motivation und Verlangen spielt, aber auch für die Vorbereitung und Kontrolle von motorischen Handlungen und Entscheidungsfindung relevant ist (Fried et al., 1991; Smolka et al., 2006; Plassmann et al., 2010; Harsay et al., 2011). In Bezug auf Pruritus wird dieses Netzwerk

besonders mit dem Wunsch zu kratzen assoziiert (Mochizuki & Kakigi, 2015). Es scheint allerdings speziell bei Patienten mit Hauterkrankungen für visuell induzierten Pruritus von Bedeutung zu sein. Eine gesteigerte Aktivität des Netzwerks konnte bei Hautgesunden während visuell induziertem Pruritus nicht nachgewiesen werden (Holle et al., 2012). Patienten mit chronischem Juckreiz scheinen während des Pruritusерlebens oder Kratzens hingegen im Vergleich zu hautgesunden Kontrollpersonen eine Überaktivität in Teilen des Netzwerks, nämlich dem SMA und den Basalganglien, aufzuweisen. Dies zeigte sich in Studien, in denen allerdings nicht pruritogen-frei Pruritus induziert wurde (Schneider et al., 2008; Ishiuji et al., 2009; Mochizuki et al., 2015). Die Untersuchung dessen, ob Patienten mit Pruritusproblematik im Vergleich zu hautgesunden Kontrollen eine Überaktivität des frontrostriatalen Netzwerks auch während visueller Pruritusinduktion zeigen, ist deswegen ein interessanter nächster Schritt. Es sollte zudem geprüft werden, ob High-Responder, also Personen, die auf visuelle Pruritusstimuli mit profunden Anstiegen im Pruritus und exzessivem Kratzverhalten reagieren, eine stärkere Aktivität im fronto-striatalen Netzwerk aufweisen als Low-Responder.

Ein zu beachtendes Nebenergebnis der Studien zur Validierung der pruritogen-freien Pruritusinduktionsmethode war die Erkenntnis, dass die Intensität des induzierten Pruritus nur dann mit Histamin-induziertem Pruritus vergleichbar ist, wenn vor der Induktion eine attentionale Fokussierung auf die Haut stattfindet. Dies weist darauf hin, dass der Aufmerksamkeitslenkung auf die Haut hier eine besondere Rolle zukommt. Bei den bis hierhin untersuchten hautgesunden Probanden musste diese Aufmerksamkeit explizit durch Priming geweckt werden. Zahlreiche Studien bei Patienten mit dermatologischen Erkrankungen verdeutlichen allerdings, dass diese eine vermehrte Aufmerksamkeit auf ihren Körper und speziell auf ihre Haut aufgrund von Stigmatisierungserfahrungen- und erleben bereits in sich tragen (Ginsburg & Link, 1993; Hawro et al., 2017; Hrehorów et al., 2012; Jankowiak et al., 2020; Kelly et al., 2021; Kowalewska et al., 2020; Krüger et al., 2014; Krüger & Schallreuter, 2015; Łakuta et al., 2018; Magin et al., 2008a; Pahwa et al., 2013; Schielein et al., 2020; Schmid-Ott et al., 2007; Soliman, 2020; Thompson et al., 2010; Vardy et al., 2002; Wahl et al., 2002; Wan et al., 2020; Wu & Cohen, 2019; Zhang et al., 2021). Passend hierzu weisen Patienten mit dermatologischen Erkrankungen in einigen (Magin et al., 2006; Magin et al., 2008b), allerdings nicht allen Studien (Schut et al., 2014; Schut et

al., 2018; Schut et al., 2015b) eine erhöhte Selbstaufmerksamkeit auf. Untersuchungen belegen bei Patienten mit sichtbaren dermatologischen Erkrankungen zudem größtenteils einen intensiveren Aufmerksamkeitsfokus auf krankheitsbezogene Stimuli im Vergleich zu hautgesunden Probanden (Fortune et al., 2003; Lee et al., 2014; Stangier et al., 2008; van Beugen et al., 2016; Willebrand et al., 2002). Die vorliegenden Studien könnten also ein indirekter Hinweis darauf sein, dass Patienten mit dermatologischen Erkrankungen besonders anfällig für audio-visuelle Pruritusstimulationen, auch im Alltag, sind. Studienergebnisse untermauern diese Hypothese: Sowohl in eigenen Arbeiten als auch in Arbeiten anderer Arbeitsgruppen reagierten Patienten mit dermatologischen Erkrankungen im Labor intensiver auf (audio-)visuelle Pruritustrigger als Hautgesunde (Kamber et al., 2020; Niemeier et al., 2000; Papoiu et al., 2011b; Schut et al., 2014; Swithenbank et al., 2016). Dies ist ein Hinweis darauf, dass sie auch im Alltag empfindlicher für solche Provokationen sein sollten. Zukünftige Forschungsarbeiten sollten sich dieser Frage gezielt zuwenden.

Eine Sensibilisierung für audio-visuell induzierten Pruritus bei Patienten mit dermatologischen Erkrankungen hat wichtige klinische Implikationen. Eine Möglichkeit besteht darin, die attentionale Fokussierung der Patienten auf die Haut und speziell auf Pruritusstimuli durch niederschwellige psychologische Interventionen, z.B. Aufmerksamkeitstrainings („Attentional bias modification (ABM) training“) zu verändern. ABM-Trainings wurden bereits mehrfach zur Reduktion von Schmerzen eingesetzt und zeigten hier widersprüchliche Ergebnisse bezüglich der Effektivität (Carleton et al., 2020; Heathcote et al., 2018; Sharpe et al., 2012; Shiasy et al., 2020; van Ryckeghem et al., 2018). In der bislang einzigen Studie zur Modifikation von Pruritus mittels ABM-Training (van Laarhoven et al., 2021) zeigten sich bei hautgesunden Probanden keine Effekte auf die attentionale Fokussierung bezogen auf Pruritusstimuli und die Intensität von mechanisch induziertem Pruritus (van Laarhoven et al., 2021). Weitere Studien sollten daher prüfen, inwiefern ein ABM-Training bei Patienten mit dermatologischen Erkrankungen Pruritus reduzieren kann. In solch einer Studie könnte wieder die Methode der audio-visuellen Pruritusinduktion genutzt werden, um möglichst realitätsnah Pruritus an vielen Körperstellen zu induzieren.

Neben der Identifikation von Gehirnregionen, welche bei visuell induziertem Pruritus aktiviert sind, war es ein weiteres Ziel der Studie Zusammenhänge zwischen der

Intensität des induzierten Pruritus und der Aktivität bestimmter Gehirnregionen zu untersuchen. Hierzu zeigte sich, dass visuell induzierter Pruritus tendenziell positiv mit der Aktivität im (Prä-)Cuneus, im posterioren Operculum (pOPC) und temporalen Kortex assoziiert war. Interessanterweise war in einer Vorgängerstudie (Ishiuji et al., 2009) der Präcuneus, der ähnlich wie der temporale Kortex für den Abruf von Gedächtnisinhalten bedeutsam zu sein scheint (Cavanna & Trimble, 2006; Palombo et al., 2015), nur bei Patienten mit chronischem Pruritus, nicht aber bei hautgesunden Kontrollprobanden während der Verarbeitung von Pruritusstimuli aktiviert. Dies lässt die Überlegung zu, dass der Anblick einer anderen Person, die sich kratzt, bei Patienten mit chronischem Pruritus Erinnerungen an selbst erlebte, Pruritus induzierende Situationen weckt, in denen sie auf Pruritus mit Kratzverhalten reagierten. Dies könnte sich im Folgenden auf die Aktivität des OPC als Schlüsselregion somatosensorischer Verarbeitung ausgewirkt haben (Garcia-Larrea, 2012; Mochizuki & Kakigi, 2015; Yosipovitch et al., 2008). Darüber hinaus wurde eine Aktivierung des Präcuneus auch mit Empathie in Verbindung gebracht (Farrow et al., 2001). In Bezug auf die eigene Studie ist Folgendes denkbar: Personen, die sich aufgrund ausgeprägter Empathie – einhergehend mit einer gesteigerten Aktivität des Präcuneus – sehr gut in die Situation der beobachteten Person hineinversetzen können und neben den Emotionen der beobachteten Person auch deren Sinnesqualitäten nachempfinden, reagieren auf das Stimulusmaterial mit stärker ausgeprägtem Pruritus, welches sich wiederum auf die Aktivität des OPC niederschlägt.

3.1.2 Moderatoren der Reagibilität auf audio-visuelle Pruritusstimuli

Das Hauptziel der Habilitationsschrift war es, psychologische Variablen als Moderatoren für audio-visuell induzierten Pruritus zu identifizieren. Als potentielle Moderatorvariablen wurden Persönlichkeitsfaktoren, Selbstaufmerksamkeit, Angst und Depression (Schut et al., 2014; Schut et al., 2015b; Schut et al., 2018) sowie die Erwartungshaltung (Schut et al., 2016) untersucht.

Den robustesten Prädiktor für induziertes Kratzverhalten bei Patienten mit dermatologischen Erkrankungen stellte der Persönlichkeitsfaktor Verträglichkeit dar: In allen drei Studien (Schut et al., 2014; Schut et al., 2015b; Schut et al., 2018), in

denen dieser Persönlichkeitsfaktor gemessen wurde, war er in der Gruppe der Patienten signifikant mit induziertem Kratzverhalten assoziiert. Die Zusammenhänge waren moderat bis groß (Cohen, 2013). Wenig verträgliche ND- und PS-Patienten wiesen folglich mehr induziertes Kratzverhalten auf als verträglichere Patienten, denen Eigenschaften wie Kooperationsfähigkeit, Empathie, Großzügigkeit, Freundlichkeit, Höflichkeit, Rücksichtnahme, geringe Feindseligkeit sowie geringe Erregbarkeit zugeschrieben werden (Caspi et al., 2005; Smith et al., 2004). Gerade die letzten Attribute sind für die Interpretation der eigenen Ergebnisse bedeutsam. Es ist möglich, dass wenig verträgliche Personen auf die Präsentation der Pruritusstimuli mit stärkerer Erregung reagieren, welche sich in Selbstberührung äußert. Hierzu passend zeigten Affen nach negativen, sozialen Interaktionen, welche sicherlich zu innerlicher Anspannung führten, vermehrt körperbezogenes Verhalten, zu dem auch das Kratzen zählt (Kutsukake & Castles, 2001). Ebenso wiesen ND-Patienten nach Stressinduktion mehr induziertes Kratzverhalten an nicht-manipulierten Hautstellen auf als während der Kontrollbedingung (Mochizuki et al., 2019). In zukünftigen Studien sollte die Hypothese, dass erhöhte Anspannung Kratzverhalten verstärkt, näher beleuchtet werden.

Es sei an dieser Stelle auch auf moderate positive Zusammenhänge zwischen Empathie und Verträglichkeit verwiesen (Melchers et al., 2016). Es mag nämlich verwundern, dass zuvor positive Zusammenhänge zwischen induziertem Pruritus und Empathie als einer Eigenschaft, die mit der Aktivität des Präcuneus in Zusammenhang steht, vermutet wurden, dass in den Studien zur Identifikation von psychologischen Variablen als Moderatoren von induziertem Pruritus aber die wenig verträglichen Patienten, die typischerweise auch weniger empathisch sind, vermehrt Kratzverhalten zeigten. Dieses Ergebnis, das auf den ersten Blick paradox erscheint, lässt sich womöglich darüber erklären, dass induzierter Pruritus und induziertes Kratzverhalten nicht signifikant miteinander korreliert sein müssen (Schut et al., 2014). Verhaltensweisen, die bei Personen mit hoher Verträglichkeit auftreten, könnten bei Patienten mit chronisch juckenden Hauterkrankungen zwar zu mehr Pruritus führen, gleichzeitig aber auch zur funktionalen Bewältigung von üblicherweise Kratzverhalten auslösenden Situationen beitragen. In diesem Zusammenhang ist bemerkenswert, dass, auch wenn in der ersten Studie das Gegenteil der Fall war (Schut et al., 2014), in immerhin zwei der drei durchgeführten Studien (Schut et al., 2015b; Schut et al.,

2018) die Patientengruppe signifikant bzw. tendenziell signifikant höhere Werte in der Skala „Verträglichkeit“ aufwies als die hautgesunde Kontrollgruppe. Verhaltensweisen zu zeigen, die mit Verträglichkeit einhergehen, können somit als Coping-Mechanismus angesehen werden. Es ist möglich, dass Patienten aufgrund ihrer Erfahrung, die sie mit Pruritus auslösenden Situationen während ihres Lebens gemacht haben, eine Persönlichkeit entwickeln, die sich nicht mit impulsivem, in gewisser Weise autoaggressivem Verhalten vereinbaren lässt. Zukünftige Studien sollten diesen postulierten Zusammenhang zwischen Empathie und (induziertem) Kratzverhalten näher beleuchten. Sollte sich herausstellen, dass Empathie ein Moderator des Kratzverhaltens ist, ergäben sich hieraus neue Interventionsmöglichkeiten.

Verträglichkeit war – wie bereits gesagt – der einzige Persönlichkeitsfaktor, der in allen drei durchgeführten Studien einen signifikanten Prädiktor für induziertes Kratzverhalten bei Patienten darstellte. Für die weiteren Faktoren aus dem Big-Five-Modell der Persönlichkeit, Angst, Depression und Selbstaufmerksamkeit ließen sich hingegen keine robusten Zusammenhänge mit induziertem Pruritus bzw. Kratzverhalten zeigen. Eine Erkenntnis der Arbeiten besteht somit auch darin, dass andere psychologische Faktoren als Verträglichkeit diagnostisch vernachlässigt werden dürfen, wenn es darum geht, psychologische Faktoren als Prädiktoren für realitätsnahen Pruritus bzw. Kratzverhalten zu identifizieren.

Ziel zukünftiger Interventionsstudien sollte es aber sein, den Pruritus-Kratz-Zirkel durch die Reduktion von mit geringer Verträglichkeit assoziierten Verhaltensweisen (z.B. feindseliges Verhalten, mangelnde Kooperationsbereitschaft oder erhöhte Aggressivität) zu durchbrechen. Interventionen, die diesbezüglich Effekte erzielen könnten, und deren Anwendung bereits mit einer Verringerung von basalem Kratzverhalten und Pruritus einherging, sind Trainings mit Bausteinen aus dem Bereich der kognitiven Verhaltenstherapie sowie Entspannungstrainings (Bae et al., 2012; Ehlers et al., 1995; Lavda et al., 2012; Schut et al., 2016a; Evers et al., 2016). Effekte von Trainings zur Erhöhung der sozialen Kompetenz (z.B. Hinsch & Pfingsten, 2008) auf Pruritus und Kratzverhalten wurden bislang noch nicht untersucht, könnten aber ebenfalls eine gute Ergänzung zu medikamentöser Therapie darstellen, da sie sich auf die Verträglichkeit auswirken (Glinski & Page, 2010). Ein weiterer gewinnbringender Ansatz, um speziell das Kratzverhalten während audio-visueller

Pruritusinduktion zu verringern, könnte die Teilnahme an einem Habit-Reversal-Training (HRT) sein, bei welchem Patienten lernen, funktionalere Verhaltensweisen an die Stelle des Kratzens treten zu lassen (Azrin & Nunn, 1973). Diese Art von Training erwies sich in mehreren Studien als effektiv, um Kratzverhalten bei ND-Patienten zu reduzieren (Rosenbaum & Ayllon, 1981; Norén, 1995; Melin et al., 1986; Norén & Melin, 1989; Norén et al., 2018). Effekte auf audio-visuell induziertes Kratzverhalten wurden bislang allerdings noch nicht untersucht, weswegen dies ein Ziel zukünftiger Studien sein sollte. Auch ist es denkbar, durch die Teilnahme an achtsamkeitsbasierten Interventionen Effekte auf das Kratzverhalten zu erzielen, indem Patienten lernen, kontrollierter und weniger automatisiert auf Pruritus zu reagieren. Dies sollte sich mittelfristig in einem besseren Hautzustand niederschlagen. Effekte von achtsamkeitsbasierten Interventionen auf den Hautzustand, nicht aber auf Pruritus bzw. Kratzverhalten, wurden bereits mehrfach (Fordham et al., 2015; Maddock et al., 2019; Kabat-Zinn et al., 1998; Meneo et al., 2022), aber nicht durchgehend (D'Alton et al., 2019) gezeigt. Lediglich eine sehr aktuelle Studie (Harfensteller, 2022) hatte das Ziel, bei ND-Patienten die Effekte der Teilnahme an einer achtsamkeitsbasierten Intervention auf Pruritus zu untersuchen. Die größten Effekte fanden sich hier auf die affektive Komponente des Symptoms. Da es sich bei dieser Arbeit allerdings um eine einarmige Studie handelte, an der nur sehr wenige Probanden teilnahmen, sind zunächst weitere Studien höherer Qualität notwendig, bevor Schlüsse bezüglich der Effekte achtsamkeitsbasierter Interventionen auf Pruritus/ Kratzverhalten bei Patienten mit chronischem Pruritus gezogen werden können. In diesen Studien könnte wieder die Methode pruritogen-freier Pruritusinduktion genutzt werden, um Pruritus/ Kratzverhalten realitätsnah zu induzieren.

Die Studie, die zur Überprüfung dessen diente, ob die Erwartungshaltung einen signifikanten Moderator für induzierten Pruritus und induziertes Kratzverhalten darstellt, zeigte abermals nur Effekte in der Gruppe der ND-Patienten, nicht aber in der Gruppe der hautgesunden Kontrollprobanden: Patienten, die realistische Informationen bezüglich der Potenz der Stimuli Pruritus zu induzieren, erhielten, wiesen anschließend signifikant weniger induzierte Kratzbewegungen und eine geringere, induzierte Kratzdauer auf als Probanden, die diese Information nicht erhielten. Eine katastrophisierende Information veränderte das Kratzverhalten nicht

signifikant. Deskriptiv ließ sich aber erkennen, dass eine katastrophisierende Vorabinformation hinsichtlich der Potenz der präsentierten Stimuli, Pruritus zu induzieren bei den Patienten mit mehr Kratzbewegungen, nicht aber einer längeren Kratzdauer, einherging als eine realistische Information. Somit bestätigt die eigene Studie einerseits, dass induziertes Kratzverhalten im Labor von Erwartungen bezüglich der verabreichten Stimuli abhängt (Sölle et al., 2021). Andererseits schließt sie die bislang vorhandene Wissenslücke zu Effekten verbaler Suggestionen auf pruritogen-frei induziertes Kratzverhalten bei Patienten mit chronischem Pruritus (Krefting et al., 2022; Meeuwis et al., 2020). Effekte verbaler Suggestionen auf pruritogen-frei induzierten Pruritus wurden zwar kürzlich untersucht, allerdings wiederum nur bei hautgesunden Probanden. Hier zeigte sich – passend zu den Ergebnissen der eigenen Studie – dass mittels Darbietung von Kratzgeräuschen induzierter Pruritus bei Personen ohne Pruritusproblematik nicht signifikant von verbalen Suggestionen beeinflusst wird (Meeuwis et al., 2022).

Aus den Ergebnissen lässt sich ableiten, dass Ärzte in Gesprächen mit Patienten über Pruritus – ähnlich wie bei Schmerz (Hasenbring & Verbunt, 2010) – realistisch über die zu erwartende Intensität des Symptoms aufklären sollten. Sowohl eine Bagatellisierung als auch Katastrophisierung der zu erwartenden Pruritusintensität gilt es hingegen zu vermeiden, wenn es darum geht, Kratzverhalten zu minimieren. Dieses Vorgehen ist in Übereinstimmung mit Ergebnissen aktueller Querschnittsstudien, die eine positive Korrelation zwischen übertriebenen, negativen Kognitionen in Bezug auf Pruritus und der Pruritusintensität, -dauer und -häufigkeit bei dermatologischen Patienten fanden (Lüßmann et al., 2021; Granot et al., 2021). Ebenso passend zeigte eine Studie, dass Stress bei ND-Patienten nur dann mit einer Steigerung der Pruritusintensität einhergeht, wenn er zu negativen Pruritus bezogenen Gedanken führt (Schut et al., 2015c). Dysfunktionale Gedanken in Bezug auf Pruritus sollten deswegen also möglichst gar nicht erst aufkommen oder aber bei Vorhandensein reduziert werden. In Übersichtsarbeiten zum Umgang mit Nocebo-Effekten bei Pruritus (Evers, 2017; Tekampe et al., 2018) wird diesbezüglich dazu geraten, den Informationsgehalt im Arzt-Patient-Gespräch an den kognitiven Bewältigungsstil des Patienten anzupassen sowie eine vertrauensvolle Arzt-Patient-Beziehung zu schaffen, in der sich der Patient ernst genommen fühlt und sich traut seine Sorgen anzusprechen, damit ihm diese anschließend durch das Gespräch mit dem Arzt

genommen werden können. Diese vorgeschlagene Vorgehensweise wurde bislang allerdings noch nicht in klinischen Studien untersucht. Ziel zukünftiger Studien sollte es somit sein, Effekte unterschiedlicher Interventionen im klinischen Setting zu prüfen. Diese können Aufschluss darüber geben, inwiefern unterschiedliche Arten der Informationsvermittlung klinisch bedingten Pruritus bzw. Kratzverhalten verändern.

3.2 Fazit

Die Arbeiten, die in diese Habilitationsschrift eingingen, dienten der Validierung einer pruritogen-freien Methode der Pruritusinduktion sowie der Identifikation psychologischer Variablen als Moderatoren der Reagibilität auf diese Methode. Sie zeigten, dass maximaler Pruritus, induziert über die Präsentation audio-visueller Stimuli, bei hautgesunden Probanden ähnlich intensiv ist wie mittels Histamin-Iontophorese induzierter Pruritus, wenn zuvor eine attentionale Fokussierung auf die Haut stattgefunden hatte und dass bei ND-Patienten während visueller Pruritusinduktion der SMA, der rechte OFC und das linke Striatum aktiviert sind. Diese Gehirnareale sind auch bei pruritogen-induziertem Pruritus relevant. Die pruritogen-freie Methode der Pruritusinduktion stellt somit eine Alternative zur Pruritusinduktion mittels pruritogener Stoffe dar. Sie kann vor allem dann genutzt werden, wenn Pruritus unabhängig von Schmerz und realitätsnah induziert werden soll. Bei der Nutzung dieser Methode ist zu beachten, dass induzierter Pruritus und Kratzverhalten durch psychologische Variablen verändert werden. Als robustester Prädiktor für audio-visuell induziertes Kratzverhalten erwies sich der Big-Five-Persönlichkeitsfaktor Verträglichkeit, der in drei Studien bei dermatologischen Patienten signifikant negativ mit induziertem Kratzverhalten assoziiert war. Die Ergebnisse legen somit nahe, dass vor allem diese psychologische Variable bei der Diagnostik des Pruritus berücksichtigt werden sollte. Bezüglich der Erwartungshaltung erwies sich eine realistische Vorabinformation als am effektivsten, wenn es darum ging, audio-visuell induziertes Kratzverhalten bei Patienten mit Pruritusproblematik zu verhindern. Aus den zuletzt genannten Studien ergeben sich neue Forschungsideen, die darauf abzielen, bei bestimmten Patienten, nämlich denen mit niedrigen Verträglichkeitswerten, mit Verträglichkeit assoziiertes Verhalten als funktionale Bewältigungsstrategie zu steigern sowie auf Ärzteseite die Effekte unterschiedlicher Arten von Informationsvermittlung im klinischen Setting zu überprüfen.

4. Zusammenfassung

Pruritus ist eine unangenehme Körperempfindung, die gemäß Definition mit dem Wunsch des Kratzens einhergeht (Hafenreffer, 1660). Man unterscheidet akuten von chronischem (> 6 Wochen) Pruritus (Ständer et al., 2007). Pruritus ist ein sehr häufiges Symptom in der Dermatologie. Chronischer Pruritus betrifft rund 37% der Patienten mit dermatologischen Erkrankungen (Schut et al., 2019) und geht mit einer hohen psychischen Belastung einher (Dalgard et al., 2020). Wichtig ist, dass sich Pruritus oft nicht allein über die Schwere der zugrundeliegenden Hauterkrankung erklären lässt (Verhoeven et al., 2008). Das biopsychosoziale Modell des Pruritus berücksichtigt neben biologischen Faktoren deswegen auch psychologische und soziale Faktoren, die zur Juckreizintensität beitragen (Verhoeven et al., 2008).

Es existieren unterschiedliche Methoden, um Pruritus standardisiert im Labor zu induzieren (Hawro et al., 2019). Die am häufigsten genutzte Substanz ist Histamin (Andersen et al., 2015; LaMotte et al., 2014). Die Applikation pruritogener Substanzen auf unterschiedlichen Wegen macht eine direkte Hautmanipulation notwendig, was Unwohlsein auslösen kann. Da negative Emotionen wie Angst als Triggerfaktor von Pruritus betrachtet werden (Sanders & Akiyama, 2018), sollten diese möglichst während der Induktion von Pruritus vermieden werden. Zudem ist die Induktion von Pruritus mittels Pruritogenen nicht mit dem vergleichbar, was bei Patienten mit Hauterkrankungen im Alltag Pruritus auslöst. Die Studien dieser Habilitationsschrift hatten daher das Ziel, eine pruritogen-freie Methode der Pruritusinduktion zu validieren und psychologische Faktoren als Moderatoren für pruritogen-frei induzierten Pruritus zu identifizieren.

In der ersten Studie (Marzell et al., 2020) zeigte sich, dass bei hautgesunden Personen durch audio-visuelle Stimuli induzierter Pruritus bezüglich seiner maximalen Intensität vergleichbar mit Histamin-induziertem Pruritus ist. Dies war allerdings nur dann der Fall, wenn zuvor eine attentionale Fokussierung auf die Haut stattfand. Auch ergaben sich Unterschiede in der Qualität und Lokalisation des Pruritus: Histamin-induzierter Pruritus war stärker oberflächlich lokalisiert, auf die Stelle der Induktion begrenzt und wurde als beißender, brennender, schmerzhafter und stechender beschrieben als audio-visuell induzierter Pruritus. In der zweiten Studie (Schut et al., 2017) zur neuronalen Grundlage von visuell induziertem Pruritus bei ND-Patienten zeigte sich, dass visuell induzierter Pruritus zu einer Aktivität in Gehirnarealen führt, die auch bei

der Verarbeitung von pruritogen-induziertem Pruritus aktiviert sind. Es kam zu einer Aktivierung in Teilen des fronto-striatalen Netzwerks: im SMA, rechten OFC und linken ventralen Striatum. Zudem war die Intensität des induzierten Pruritus positiv mit der Aktivität im Präcuneus, temporalen Kortex und pOPC assoziiert. Die Ergebnisse der ersten beiden Studien (Marzell et al., 2020; Schut et al., 2017) legen somit nahe, dass es sich bei der Präsentation von audio-visuellen Pruritusstimuli um eine gute Alternative zu pruritogenen Substanzen handelt.

In drei weiteren Studien (Schut et al., 2014; Schut et al., 2018; Schut et al., 2015b) wurde bei Patienten mit dermatologischen Hauterkrankungen, nicht aber bei hautgesunden Kontrollen, der Persönlichkeitsfaktor Verträglichkeit als robuster Moderator von audio-visuell induziertem Kratzverhalten identifiziert. Es ergaben sich signifikante, negative moderate bis große Zusammenhänge zwischen der Anzahl der induzierten Kratzbewegungen und der Ausprägung dieses Persönlichkeitsfaktors. Selbstaufmerksamkeit und Depression zeigten sich vereinzelt, nicht aber über alle Studien hinweg, signifikant positiv mit induziertem Pruritus oder Kratzverhalten assoziiert. Die vierte Studie (Schut et al., 2016) untersuchte, inwiefern Vorinformationen zu im Nachhinein präsentierten Pruritusstimuli den induzierten Pruritus und das induzierte Kratzverhalten verändern. Es zeigten sich Effekte abermals nur in der Gruppe der ND-Patienten: Patienten, die eine realistische Information bezüglich der Pruritusstimuli erhalten hatten, zeigten während der Pruritusinduktion signifikant weniger Kratzbewegungen und eine kürzere Kratzdauer als Personen, die vorab keine Informationen zu den Pruritusstimuli erhalten hatten. Somit hatte das Weglassen von Informationen negative Effekte auf Kratzverhalten. Diese Ergebnisse sind klinisch relevant, da sie Informationen dazu liefern, wie wichtig es ist, Patienten realistisch über die Symptome ihrer Krankheit aufzuklären und welche Interventionen ihnen helfen können, funktionaler mit Pruritus umzugehen.

5. Summary

Pruritus is an unpleasant bodily sensation, which – according to the definition – is accompanied by the desire to scratch (Hafenreffer, 1660). It is distinguished between acute and chronic pruritus, i.e. pruritus lasting longer than six weeks (Ständer et al., 2007). Pruritus is a very common symptom in dermatology. Chronic pruritus affects 37% of patients with dermatologic diseases according to a European multicenter study (Schut et al., 2019) and is associated with a high psychological burden (Dalgard et al., 2020). Importantly, pruritus often cannot be explained by the severity of the underlying skin disease alone (Verhoeven et al., 2008). The biopsychosocial model of pruritus therefore considers psychological and social factors that contribute to itch intensity in addition to biological factors (Verhoeven et al., 2008).

Different methods exist to induce pruritus in a standardized manner in the laboratory (Hawro et al., 2019). The most commonly used substance is histamine (Andersen et al., 2015; LaMotte et al., 2014). The application of pruritogenic substances by different routes necessitates direct skin manipulation, which may induce discomfort in subjects. Since negative emotions such as anxiety are considered as trigger factors of pruritus (Sanders & Akiyama, 2018), they should be avoided as much as possible during pruritus induction. In addition, pruritus induction using chemical substances is less comparable to what triggers pruritus in patients with skin diseases in everyday life than the presentation of audio-visual pruritus stimuli. Therefore, the studies in this postdoctoral thesis aimed to validate a pruritogen-free method of pruritus induction and to identify psychologic factors as moderators of pruritogen-free induced pruritus.

The first study (Marzell et al., 2020) showed that in skin healthy subjects, pruritus induced by audio-visual stimuli was comparable to histamine-induced pruritus with respect to its maximal intensity. However, this was only the case if priming was conducted before the presentation of the stimulus material. There were also differences in the quality and localization of pruritus: histamine-induced pruritus was more superficially localized, limited to the site of induction, and described as more biting, burning, painful, and stinging than audio-visually induced pruritus.

The second study (Schut et al., 2017) investigated the neural basis of visually induced pruritus in patients with atopic dermatitis. It was shown that visually induced pruritus leads to activity in brain areas that are also activated during the processing of pruritogen-induced pruritus. Activation occurred in parts of the frontriostriatal network: in the SMA, right OFC, and left ventral striatum. In addition, the intensity of induced pruritus was positively associated with activity in the precuneus, temporal cortex, and pOPC. The results of these first two studies (Marzell et al., 2020; Schut et al., 2017) suggest that the presentation of audio-visual pruritus stimuli is a good alternative to the application of pruritogens.

In three other studies (Schut et al., 2014; Schut et al., 2018; Schut et al., 2015b), the personality factor agreeableness was identified as robust moderator of audio-visually induced scratching behavior in patients with dermatological skin diseases, but not in healthy skin controls. Significant negative moderate to large correlations emerged between the number of induced scratching movements and the expression of this personality factor. Self-consciousness and depression showed significant positive associations with induced pruritus or scratching behavior only occasionally, but not across all studies. The fourth study (Schut et al., 2016) examined the extent to which prior information about subsequently presented pruritus stimuli altered induced pruritus and induced scratching behavior. Again, effects were found only in the group of ND patients and not in the control group: patients who had received realistic information regarding upcoming pruritus stimuli showed significantly fewer scratching movements and a shorter scratching duration during pruritus induction than subjects who had not received any information regarding the pruritus stimuli in advance. Thus, omitting information had negative effects on scratching behavior. These findings are clinically relevant, because they provide information about the importance of educating patients about their symptoms in a realistic way and regarding what psychological interventions can help to cope with pruritus in a more functional way.

6. Literatur

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7. Anhang

7.1 Abkürzungsverzeichnis

ABM	Attentional Bias Modification
EV	Experimentalvideo
HRT	Habit-Reversal-Training
k	Cluster-Größe
KV	Kontrollvideo
ND	Neurodermitis
OFC	Orbitofrontalkortex
pOPC	Posteriores Operculum
PS	Psoriasis
SI	Primärer somatosensorischer Kortex
SII	Sekundärer somatosensorischer Kortex
SEM	Standardfehler
SMA	Supplementäres Motorareal
VAS	Visuelle Analogskala
x	Mittelwert

7.2 Abbildungsverzeichnis

7.3 Publikation 1

Marzell R, Kupfer J, Reichwein G, Gieler U, **Schut C*.** Itch induction by audiovisual stimuli and histamine iontophoresis: a randomized, controlled non-inferiority study. *British Journal of Dermatology* 2020;182:1253-1261; doi: 10.1111/bjd.18368; * korrespondierende Autorin;

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GENERAL DERMATOLOGY

BJD
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Itch induction by audiovisual stimuli and histamine iontophoresis: a randomized, controlled noninferiority study*

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Summary

Background Previous research has mainly used skin-manipulating methods to induce itch. In comparison, itch induced by audiovisual stimuli lacks direct skin manipulation.

Objectives The aim of this double blind, noninferiority study was to test the experimental hypothesis that itch induced by audiovisual stimuli is noninferior to itch induced by histamine iontophoresis in case of priming and without priming.

Methods In 80 of 160 healthy volunteers itch was induced by histamine iontophoresis, while in the other 80 itch was induced by audiovisual stimulation. Forty people in each group experienced either an initial resting phase or dermal priming. Itch intensity was measured by visual analogue scales, while scratch duration and frequency were video-recorded and evaluated by two independent raters. In addition, itch quality and location were measured by self-report.

Results Itch induced by audiovisual stimuli was inferior to itch induced by histamine iontophoresis in the absence of dermal priming. However, in the case of priming, maximal itch induced by audiovisual stimuli was not inferior to maximal itch induced by histamine iontophoresis. Additionally, differences in itch quality and location were observed.

Conclusions The finding that maximal audiovisually-induced itch was comparable with maximal histamine itch only after priming emphasizes that attention plays a dominant role in mentally-induced itch. The comparability of maximal histamine and audiovisually-induced itch in the case of priming opens up new research opportunities.

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What's already known about this topic?

- Itch is a multidimensional sensation that is altered by, among other things, attention.
- To induce itch in basic research, different methods are used, which are partially invasive or cause skin manipulation.
- Noninvasive audiovisual stimuli can be used to induce itch.

What does this study add?

- This study investigated whether itch induced by audiovisual stimuli is noninferior to itch induced by histamine iontophoresis.
- Itch induced by audiovisual stimuli is noninferior with regard to maximal intensity in the case of priming.
- Noninferiority was not shown in the case of no priming, emphasizing the role of attention in itch induction.
- Histamine and audiovisually-induced itch differ in terms of quality and location, but not in affective reaction.

Itch is an unpleasant sensation triggering scratching or the urge to do so.[1] Psychological factors are linked to its intensity.[2–4]

Physical and psychological methods are available to induce itch in laboratory settings. The former are well established but need the skin to be manipulated. Skin manipulation itself can be unpleasant, possibly resulting in anxiety, which is supposed to affect itch sensation.[5] Thus, itch induction including skin manipulation might increase itch perception not only through the applied substance, but also, for example, by triggering anxiety. Furthermore, an attentional focus on physical sensations is linked to an increased experience of itch.[6]

Itch induction by histamine iontophoresis is based on the lococutaneous effect of histamine.[7] Histamine causes the typical triad of itch, wheal and erythema by activating its receptors on itch-conducting mechanoinsensitive C fibres and the endothelium.[8–11] Using histamine iontophoresis, maximum itch intensity is usually reached after 3–4 min.[12,13] The induced itch is tickling, pricking, warm, radiating and localizable, annoying, wavelike and lasts > 15 min. The effects depend on the iontophoresis current.[12]

In addition, itch can be induced by (audio)visual stimuli,[14–18] without the need to manipulate the skin directly. Various factors are assumed to play a role in this kind of itch induction. Besides classical conditioning, mirror neurons and empathy are discussed as contributing to mentally-induced itch.[19–22] For sensations induced by substances, it has already been shown that they are altered by attention.[6,23] It is reasonable that itch induction by the presentation of audiovisual itch depends even more on the subjects' attention, as only focusing on the stimuli and the skin should have an effect. Thus, priming on the skin could be a strategy to alter audiovisually-induced itch. Indeed, in our previous studies we noticed that induced itch was more intense when a skin-related control video was shown before and not after audiovisual itch stimuli. However, we did not investigate this effect systematically.

So far, there have been studies comparing the effectiveness of different substance-dependent itch-inducing methods.[24–26] However, no study thus far has compared mental induction to substance-dependent methods. Therefore, we aimed to test whether audiovisually-induced itch is noninferior to itch induced by histamine iontophoresis. Our experimental hypothesis (H1) was not a superiority hypothesis, but a noninferiority one. Subsequently, the effect of shifting attention toward the skin (dermal priming) before itch induction was investigated.

As there have been no studies describing the quality of audiovisually-induced itch and only a few describing the quality of itch induced by histamine,[25,26] a secondary aim was to assess the quality and location of induced itch.

Patients and methods

Participants

In total, 160 healthy volunteers were recruited. Each volunteer received €20 for participation in the study. Volunteers had to be aged 18–30 years in order to be included. During an initial telephone interview, volunteers were screened for the following exclusion criteria: participation in preliminary studies at our institute; prior participation in stress-management trainings; current psychiatric/neurological diseases; chronic physical illness; use of a cardiac pacemaker; adrenal or thyroid diseases; allergies; previous anaphylactic reactions; hay fever/bronchial asthma; immune system disorders; skin diseases, infections or other current diseases; vaccinations within the last 3 months; current mosquito bites; the current use of medically indicated medications/ointments (Fig. S1; see Supporting Information).

Study design

This double-blind, randomized study consisted of two substudies. In study 1(a), 80 participants rested for 10 min (no dermal priming) before itch was induced either by histamine iontophoresis [histamine gel + neutral video 2 (NV2): control group (CG); $n = 40$; resting-histamine] or audiovisual itch stimuli [placebo gel + experimental video (EV): experimental group (EG); $n = 40$; resting-audiovisual itch]. In study 1(b) (dermal priming), all 80 participants watched a non-itch-inducing skin-related video [neutral video 1 (NV1)] before itch induction [either presentation of a non-itch-inducing NV2 + histamine iontophoresis: CG ($n = 40$; priming-histamine) or presentation of the EV + placebo gel: EG ($n = 40$; priming-audiovisual itch)]. Randomization was conducted by a person not involved in data collection by drawing a closed envelope out of a bigger envelope including a card with a number. The number informed the investigators (R.M., G.R.) which video had to be presented and what gel tube had to be applied. Groups were stratified according to age and sex. The investigators were blinded to the content of the gel and the video. To blind study participants to the study aim, they were told that 'male and female healthy participants will be randomly assigned to one of two experimental conditions (presentation of different videos and application of different substances on the skin) and will be asked to report their current bodily sensations and emotions. We are interested in whether groups differ regarding the relationship between bodily sensations and emotions'. Regarding iontophoresis, they were told that 'the experimenter will apply two electrodes to the forearm, which include a substance that can evoke, increase or reduce one or more of the sensory qualities and emotions we are interested in'. Regarding the camera, the information that 'during the investigation you will be filmed by use of a video camera in order to be able to rate your mimics and gestures during the investigation' was included in the information sheet. Participants were informed about the real intention of the study at the end of the investigation.

Recruitment and data collection took place between August 2013 and April 2014. At the beginning of the investigation, which took place at the Dermatology Clinic of the University of Giessen, each participant was seated on a leather armchair, 3·5 m from a 2 × 2 m screen and asked to remove his/her

bracelets. Then the exclusion criteria were reviewed again. Afterwards, the participant was video-recorded for 10 min while resting [study 1(a)] or being presented NV1 [study 1 (b)]. Afterwards, participants had to rate the sensations and emotions they had in the previous 10 min and at the current moment. During the subsequent itch induction period, the participant was video-recorded and afterwards, sensations and emotions were assessed again. In addition, questionnaires measuring itch characteristics and psychological variables were completed (Table 1).

Itch induction

In the CG, itch was induced by histamine iontophoresis, which was followed by a non-itch-inducing video on the skin (NV2). In the EG, itch was induced by an EV on itch, which was started after application of the placebo gel. NV2 contained nice static pictures: a baby's hand touching the hand of an adult; a naked woman and man sitting in the nature in front of a waterfall; the face of a woman taking a shower; a female and male hand almost touching each other; the faces of two Barbie dolls with perfect skin; a baby's feet and a mother's feet walking on a white blanket; two cats cuddling each other; a woman lying in a bath tub; and six feet (two from a father, four from children) under a comforter. During the presentation of the pictures, the speaker (U.G.) talked in the background about the skin as the organ of communication, the role of touching for babies, tactile sensors of the skin, the fact that humans mainly consist of water, and so on. The EV included nine static pictures: a female scratching her back; ants crawling on a white surface; a bloody mosquito bite on a hand and a mosquito; skin that was scratched after a mosquito bite; a big bug; two monkeys lousing each other; a human flea; and flea bites on a human's back (two pictures). While the pictures were displayed, the speaker (U.G.) talked about ants, mosquitos, fleas, bugs, lousing monkeys, that scratching can be a displacement activity in stressful situations, and so on. NV1 [only used in study 1(b)] contained nine static pictures: hands splashing water; a girl wearing sunglasses, a sun hat and having sun lotion on her face; five young adults with different skin types; a man looking in the mirror while putting lotion on his face; a child's hand holding a wrinkled hand; the back of a man with many naevi, being looked at through a magnifying glass by a female dermatologist; the face of a middle-aged woman with a large naevus above her upper lip; a man with a wart beneath his right eye and a young, red-haired woman with many freckles (one picture); and sunlight shining on a cornfield. In the background, a speaker (U.G.) talked about the skin in general, different skin types, sunburn, sun protection, skin screening and the need of sun.

In line with Papoiu et al.,[24] iontophoresis was performed with 2% methylcellulose gel in the EG (CG: + 1% histamine) at 200 μA for 30 s on the nonleading forearm. The electrodes [PF384 Dispersive Electrode and LI611 Drug Delivery Electrode (Perimed, Järfälla, Sweden)] were positioned 5 cm proximal to the wrist at a distance of 15 cm. The application site was cleaned before and after applying the electrodes with kodan® tincture forte colourless (Schülke, Norderstedt, Germany) and pulp. Electrodes were removed after 30 s. Immediately after removing the electrodes, either NV2 (in case of histamine application) or EV (in case of placebo gel application) was started.

Assessment of alteration in itch parameters

Maximal itch intensity during itch induction was measured by using the item, 'Please indicate to what extent the following

Table 1 Study procedure

Minute	0-10	10-20	20-23	23-38	38-50	50-60
Study 1a Study 1b	Introduction + consent	Resting (1a) Dermal priming (1b)	Questionnaires	Experimental itch induction: either **histamine iontophoresis** + presentation of non-itch inducing audiovisual stimuli **OR presentation of audiovisual itch stimuli** + placebo iontophoresis	Questionnaires	Debriefing + allowance
Measurement		Scratch movements + duration	Sense qualities and emotions including itch intensity	Scratch movements + duration	Sense qualities and emotions including itch intensity, itch qualities and affective responses to pruritus, psychosocial data, others	

statements applied to you *since the application of the gel*. Indicate the *maximal intensity* you perceived: I perceived itch'. Current itch intensity immediately after the itch induction period was measured by the item, 'Please indicate to what extent the following statement *currently* applies to you: I perceive itch'. These questions were answered on a visual analogue scale [VAS; 0 (not at all) to 10 (very intense)]. The target variable alteration in itch intensity was calculated by subtracting the values obtained from the itch induction period from the corresponding values of the resting phase/priming phase.

To measure scratch movements and scratch duration, participants were filmed during the resting/priming and itch induction periods. All video material was evaluated by two independent raters using observation software (Interact; Mangold International, Arnstorf, Germany). The raters were trained by a dermatologist (U.G.) on differentiating scratching from touching. Afterwards, determination of the number of scratch movements and scratch duration reliability analyses were conducted for both measures. These yielded significant inter-rater reliabilities (Cronbach's $\alpha \geq 0{\cdot}963$).

Assessment of itch characteristics

To assess the location of itch, participants marked the body sites where their itch began and where it spread to. Itch qualities and affective responses to itch were measured on a 5-point Likert scale [0 (not at all) to 4 (always)] by use of a German adaptation of an itch questionnaire based on the McGill pain questionnaire.[27,28]

Ethics

In conformity with the Declaration of Helsinki, the study design was approved by the local ethics committee of the medical faculty at the University of Giessen (Institutional Review Board approval #46/13). Participants were informed about possible health risks, the study procedure, expense allowance, data security and insurance. Participants were free to withdraw from the study at any time.

Statistical analysis

We aimed to show that itch-related audiovisual itch stimuli are not worse at inducing itch than histamine iontophoresis. Thus, our hypothesis (H1) was that the presentation of audiovisual itch stimuli leads to a comparable increase in itch as histamine iontophoresis. This approach is the opposite of that usually used (superiority hypotheses stating that one group/treatment is better than another).[29] We aimed to test our H1 in the case of no and in case of prior priming. As it is impossible to show exact equivalence, a prespecified margin of noninferiority was defined beforehand.[29,30] We estimated the precision of measurements by using data from our previous research and considerations regarding the standard error measurement. From previously collected data,[17,31] it was known that the mean ± SD increase in itch in healthy skin controls after having seen a non-itch-inducing control video was 2·7 ± 3·1. Another group found a retest reliability of a VAS measuring itch in patients with chronic itch 0·88.[32] A recent study confirmed the reliability of this size for acute histamine-induced itch in healthy controls (intraclass correlation coefficient 0·83–0·93).[33] Thus, the standard error of measurement was calculated as $S_e = 3{\cdot}1\sqrt{1}-0{\cdot}88 = 1{\cdot}07$. The corresponding confidence interval (CI) is $CI = x-1{\cdot}96 \times 1{\cdot}07 = x-2{\cdot}10$. Using a conservative approach, we rounded off and set the noninferiority margin a priori to −2 (VAS 0–10). A difference within this limit was interpreted as noninferiority. Taking these values into consideration, we used the following formula to calculate our sample size: $2 \times 3{\cdot}1^2(1{\cdot}96 + 0{\cdot}84)^2/(2-0)^2$.[34,35] It revealed that 38 participants had to be included in each group to achieve a power of 80% with a given α of 0·05. We recruited 40 people per group, in order to account for possible dropouts. Then noninferiority tests were performed according to Walker and Nowacki[30]: 'non-inferiority is established, at the α significance level, if the lower limit of a $(1-2\alpha) \times 100\%$ CI for the difference (new − current) is above $-\delta$', whereby $-\delta$ represents the noninferiority margin. For the manipulation check (could itch be induced by both methods?) and group comparisons t-tests and Pearson χ^2-tests were conducted using SPSS Statistics 24 (IBM, Armonk, NY, U.S.A.).

Results

Group comparison

In study 1(a) (no priming = resting), each group consisted of 11 men and 29 women.

The mean ± SD age of those in the CG (resting-histamine) was 23·78 ± 2·77 years, and that of the EG (resting-audiovisual itch stimuli) was 24·73 ± 2·53 years [$t(78) = 1{\cdot}60$; $P > 0{\cdot}05$]. Those in the EG had a significantly more intense itch compared with those in the CG during the resting period [EG 0·96 ± 1·42; CG 0·41 ± 0·80 (VAS 0–10); $t(61{\cdot}7) = 2{\cdot}14$; $P = 0{\cdot}04$]. No further group differences regarding any other itch parameters were seen.

In study 1(b) (priming), each group consisted of 18 men and 22 women. The mean ± SD age of those in the CG (priming-histamine) was 23·68 ± 2·96 years, and that of the EG (priming-audiovisual itch stimuli) was 23·80 ± 2·63 years [$t(78) = 0{\cdot}20$; $P = 0{\cdot}84$]. Apart from an initially increased level of disgust (VAS 0–10) in the CG during priming [1·14 ± 1·79 vs. 0·43 ± 0·94; $t(78) = -2{\cdot}23$; $P = 0{\cdot}03$], no further group differences occurred, neither during nor immediately after priming.

A manipulation check revealed that all itch parameters, except for scratch duration, significantly increased from the resting/priming period to itch induction period (Table 2).

Noninferiority testing

Average changes in itch intensity due to the different itch induction methods can be found in Figure 1.

Table 2 Manipulation check itch induction

Condition	Increase in maximal itch intensity (VAS 0–10)	Increase in current itch intensity (VAS 0–10)	Increase in the number of scratch movements	Increase in scratch duration (s)
Resting-audiovisual itch stimuli ($n = 40$)	2·04 ± 2·46 [T(39) = 5·23; P ≤ 0·001]	1·04 ± 1·54 [T(39) = 4·27; P ≤ 0·001]	1·14 ± 3·06 [T(39) = 2·35; P = 0·02]	2·06 ± 8·94 [T(39) = 1·46; P = 0·15]
Resting-histamine ($n = 40$)	4·46 ± 3·18 [T(39) = 8·87; P ≤ 0·001]	2·56 ± 3·10 [T(39) = 5·24; P ≤ 0·001]	1·06 ± 2·53 [T(39) = 2·65; P = 0·01]	4·00 ± 13·42 [T(39) = 1·88; P = 0·07]
Priming-audiovisual itch stimuli ($n = 40$)	2·96 ± 2·81 [T(39) = 6·67; P ≤ 0·001]	1·54 ± 2·14 [T(39) = 4·54; P ≤ 0·001]	2·28 ± 5·97 [T(39) = 2·41; P = 0·02]	5·71 ± 24·78 [T(39) = 1·46; P = 0·15]
Priming-histamine ($n = 40$)	3·15 ± 2·95 [T(39) = 6·74; P ≤ 0·001]	2·61 ± 3·31 [T(39) = 4·98; P ≤ 0·001]	2·86 ± 5·26 [T(39) = 3·44, P = 0·001]	12·67 ± 84·05 [T(39) = 0·95, P = 0·35]

Average increases in itch parameters due to itch induction (Δ values of itch induction period/values of resting or priming period, respectively). VAS, visual analogue scale.

Study 1(a): The noninferiority test showed that itch induced by audiovisual stimuli was inferior to itch induced by histamine iontophoresis in the case of no priming (mean difference of maximum induced itch −1·52, with a lower 90% CI bound of −2·43). The mean difference in current itch immediately after itch induction was −2·42 (lower bound 90% CI of −3·48). As these lower bounds of the 90% CI were outside the noninferiority margin, the noninferiority test revealed inferiority of itch induced by audiovisual stimuli vs. itch induced by histamine for study 1(a).

Study 1(b): The noninferiority test showed that maximal itch induced by audiovisual stimuli was not inferior to histamine-induced itch in case of priming, with a mean difference of induced itch of −0·183 (lower bound 90% CI of −1·26), lying within the noninferiority margin of −2. Noninferiority could not be shown for current itch immediately after the itch induction period, with a mean difference of −1·07 and a lower bound 90% CI of −2·1 (which is outside the noninferiority margin) (Fig. 2).

Location and quality of itch

Owing to the fact that noninferiority of maximal itch induced by audiovisual stimuli was only shown after priming, we focused on the comparison of histamine and audiovisually-induced itch after priming [study 1(b)] only. In contrast to a strictly localized histamine-induced itch at the site of application, itch induced by audiovisual stimuli was observed in multiple regions (Fig. 3). More participants of the CG than of the EG reported that itch began on the arms [EG: n = 14; CG: n = 34 ($\chi^2 = 20{\cdot}83$, $P < 0{\cdot}001$)], whereas itch induced by audiovisual stimuli more often than histamine induced itch began on the face [EG: n = 15; CG: n = 5 ($\chi^2 = 6{\cdot}67$, $P = 0{\cdot}01$)] or back [EG: n = 4; CG: n = 0 ($\chi^2 = 4{\cdot}21$, $P = 0{\cdot}04$)]. For the neck, chest, scalp and anogenital region, no significant differences between the groups were recorded.

In the course of the 10-min itch induction period, more participants of the EG than of the CG experienced itch on their face [EG: n = 30; CG: n = 15 ($\chi^2 = 11{\cdot}43$; $P < 0{\cdot}001$)], followed by itch on their hands [EG: n = 12; CG: n = 2 ($\chi^2 = 8{\cdot}66$, $P < 0{\cdot}01$)], legs [EG: n = 12; CG: n = 4 ($\chi^2 = 5{\cdot}00$, $P = 0{\cdot}03$)], back [EG: n = 11; CG: n = 3 ($\chi^2 = 5{\cdot}54$, $P = 0{\cdot}02$)] and feet [EG: n = 9; CG: n = 2 ($\chi^2 = 5{\cdot}17$, $P = 0{\cdot}02$)]. Histamine iontophoresis more often led to itch on the arms than audiovisually induced itch [EG: n = 26; CG: n = 40 ($\chi^2 = 16{\cdot}97$, $P < 0{\cdot}001$)]. Itch induced by both methods also frequently led to itch on the scalp [EG: n = 16; CG: n = 11 ($\chi^2 = 1{\cdot}40$, $P = 0{\cdot}24$)].

Histamine-induced itch was described as more 'biting' [t(65·71) = 2·48; P = 0·02), 'painful' [t(67·82) = −3·33; P = 0·001), 'burning' [t(78) = −2·52; P = 0·01], 'superficially localized' [t(66·71) = −2·33, P = 0·02] and 'piercing' [t(70·85) = −2·73; P = 0·01] than audiovisually-induced itch. No other group differences occurred (Fig. 4).

Discussion

As studies have shown, itch can be induced by the presentation of (audio)visual itch stimuli.[14–18,31] Our study compared itch induced by audiovisual stimuli to itch induced by histamine iontophoresis. We aimed to show that itch induced by audiovisual stimuli is not inferior to itch induced by histamine iontophoresis. We found that audiovisually-induced itch was inferior to histamine-induced itch in case of resting before itch induction (no priming). However, maximal audiovisually-induced itch after priming was comparable with itch induced by histamine iontophoresis. We speculate that attention shifting might thus be especially capable of affecting mental processes. This hypothesis is supported by the fact that an attentional bias towards itch pictures, but not for somatosensory itch stimuli, was recently shown.[23] Our study suggests that the attentional bias towards itch pictures might be strengthened by priming, resulting in noninferiority of audiovisually-induced itch vs. histamine-induced itch.

The fact that noninferiority could only be shown for the time of itch induction itself ('maximal itch during itch induction') and not for the time thereafter ('current itch after itch induction') can possibly be explained by a prolonged effect of locally applied histamine,[12] which has not yet been shown for audiovisually-induced itch. Moreover, as attention is relevant for the intensity of audiovisually-induced itch, it is possible that completing the questionnaires after the itch induction

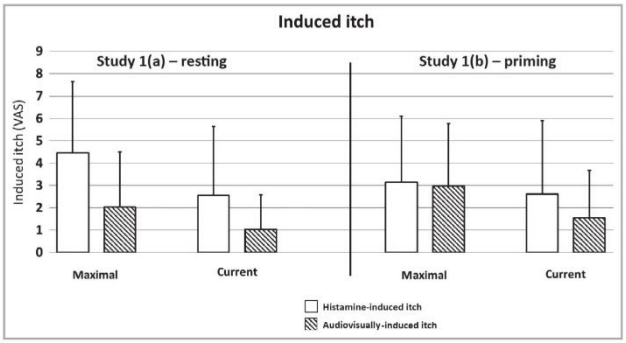

Fig 1. Itch induced by either histamine iontophoresis (white) or audiovisual stimuli (shaded), with or without priming. Maximal itch intensity during the itch induction period minus maximal itch intensity during resting (study 1a) or priming (study 1b) period; current itch intensity immediately after itch induction minus current itch intensity immediately after resting or priming period. Error bars represent the SD of the mean induced itch. VAS, visual analogue scale.

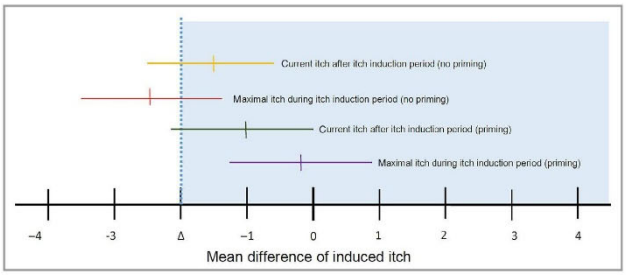

Fig 2. Observed mean differences in induced itch (audiovisually-induced itch minus histamine-induced itch). Error bars indicate two-sided 90% confidence intervals. The blue dashed line indicates the noninferiority margin (−2). The light-blue shaded area to the right of Δ indicates a noninferiority of audiovisual itch; yellow line indicates mean difference of current itch [visual analogue scale (VAS) 0–10] immediately after the itch induction period [study 1(a), no priming]; red line indicates the mean difference of maximum itch (VAS 0–10) during the itch induction period [study 1(a), no priming]; green line indicates the mean difference of current itch (VAS 0–10) immediately after the itch induction period [study 1(b), priming]; purple line indicates the mean difference of maximum itch (VAS 0–10) during the itch induction period [study 1(b), priming].

period has a more reducing effect on audiovisually-induced itch than on itch induced by histamine iontophoresis.

Itch induced by histamine iontophoresis was experienced as more biting, painful, burning, superficially localized and piercing than audiovisually-induced itch. With regard to the location of itch, histamine itch was experienced at the site of application, while itch induced by audiovisual stimuli spread from central to peripheral areas (Fig. 3). This distribution pattern is in line with the findings of other studies.[15,36] In these studies, the presentation of videos showing other people scratching mainly led to scratching of the face, head and body sites distal from the stimulated forearm.[15,36] One explanation is that audiovisual itch stimuli activate an emotion-based mirror neuron system, the activation of which results in anxiety/tension, which is then processed/reduced by displacement behaviours such as self-touching or scratching the face and other distal body sites.[20,36,37] Another explanation mentioned previously is that ongoing or spontaneous itch-related afferent activity might be overinterpreted as itch when one's attention is centred on itch-related issues.[15] Furthermore, we assume that the number of free nerve endings, illustrated by the sensory homunculus,[38] plays a role when it comes to the location of audiovisually-induced itch as high neural resolution increases the risk of spontaneous tension discharges. Our data support this assumption as audiovisually-induced itch mainly occurred in higher-resolution regions.

Interestingly, itch intensities were not significantly correlated with the number of scratch movements after priming [EG: $r = 0{\cdot}14$ ($P = 0{\cdot}20$); CG: $r = 0{\cdot}18$ ($P = 14$)]. This confirms that itch and scratching should not be regarded as co-existent, even though they – per definition – occur together.[1] Previously, small-to-moderate correlations have been

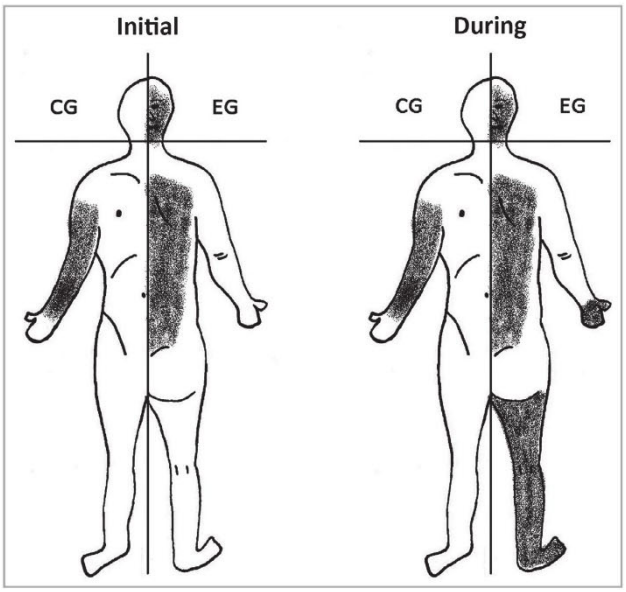

Fig 3. Typical location of induced itch. Grey areas mark the regions for which significant group differences were found regarding the number of persons who felt itch initially and in the course of the itch induction period. (Left) Body sites where itch induced by histamine and audiovisual stimuli typically began (initial); (right) body sites where itch typically occurred during the itch induction period. Left body side: control group (CG; itch induced by histamine iontophoresis); right body side: experimental group (EG; itch induced by audiovisual itch induction).

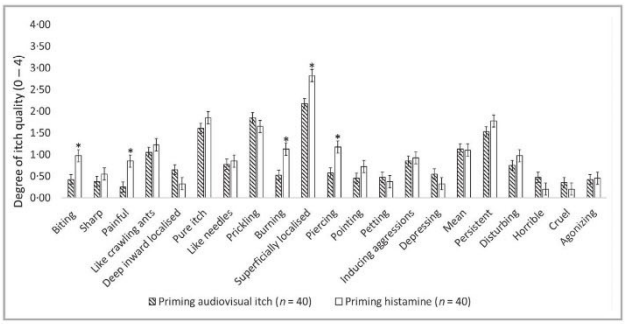

Fig 4. Differences in itch quality, induced by either audiovisual itch stimuli or histamine after priming. *Statistically significant difference ($P < 0{\cdot}05$).

observed.[16,39] A possible explanation for the rather low correlations in our study could be that some participants tried to refrain from scratching to avoid a worsening of itch, as they reported afterwards. An additional explanation is that scratching might have also occurred as displacement behaviour with the purpose of lowering tension, which might have differed between participants. The assessment of tension during itch induction should be done in future studies.

This study had some limitations. The participants were rather young and educated. In the future, the sample should be more heterogeneous. Furthermore, as we used a very unspecific manipulation (watching a video vs. resting), we cannot rule out that a mechanism other than priming led to the differences in induced itch in studies 1(a) and 1(b). It would therefore be of advantage to test the effects of dermal priming against the effects of another, more specific

manipulation (e.g. watching a video that shifts attention to another non-skin-related topic). This would also be beneficial, as in this study the baseline values for itch were generally higher in the dermal priming group. However, it is not easy to find a video not evoking positive or negative emotions, which have been shown to be associated with an altered perception of sensations.[40,41]

In conclusion, this study is the first to show that maximal itch induced by audiovisual itch stimuli is not inferior to itch induced by histamine iontophoresis, but only in case of skin-related priming. Thus, this study gives further insight into the effectivity of itch-inducing methods.

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Supporting Information

Additional Supporting Information may be found in the online version of this article at the publisher's website:

Fig S1. CONSORT flow diagram.

Powerpoint S1. Journal Club Slide Set.

7.4 Publikation 2

Schut C[+*], Mochizuki H[+], Grossman SK, Lin AC, Conklin CJ, Mohamed FB, Gieler U, Kupfer J, Yosipovitch G. Brain processing of contagious itch in patients with atopic dermatitis. *Frontiers in Psychology* 2017;8:1267. doi: 10.3389/fpsyg.2017.01267; + geteilte Erstautorenschaft; * korrespondierende Autorin;

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frontiers in Psychology

ORIGINAL RESEARCH
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Brain Processing of Contagious Itch in Patients with Atopic Dermatitis

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Several studies show that itch and scratching cannot only be induced by pruritogens like histamine or cowhage, but also by the presentation of certain (audio-) visual stimuli like pictures on crawling insects or videos showing other people scratching. This phenomenon is coined "Contagious itch" (CI). Due to the fact that CI is more profound in patients with the chronic itchy skin disease atopic dermatitis (AD), we believe that it is highly relevant to study brain processing of CI in this group. Knowledge on brain areas involved in CI in AD-patients can provide us with useful hints regarding non-invasive treatments that AD-patients could profit from when they are confronted with itch-inducing situations in daily life. Therefore, this study investigated the brain processing of CI in AD-patients. 11 AD-patients underwent fMRI scans during the presentation of an itch inducing experimental video (EV) and a non-itch inducing control video (CV). Perfusion based brain activity was measured using arterial spin labeling functional MRI. As expected, the EV compared to the CV led to an increase in itch and scratching ($p < 0.05$). CI led to a significant increase in brain activity in the supplementary motor area, left ventral striatum and right orbitofrontal cortex (threshold: $p < 0.001$; cluster size $k > 50$). Moreover, itch induced by watching the EV was by trend correlated with activity in memory-related regions including the temporal cortex and the (pre-) cuneus as well as the posterior operculum, a brain region involved in itch processing (threshold: $p < 0.005$; cluster size $k > 50$). These findings suggest that the fronto-striatal circuit, which is associated with the desire to scratch, might be a target region for non-invasive treatments in AD patients.

Keywords: contagious itch, atopic dermatitis, functional MRI, supplementary motor area, striatum, orbitofrontal cortex

INTRODUCTION

Itch is regarded as unpleasant and provokes the desire to scratch (Savin, 1998). Many patients with skin diseases suffer from this symptom on a regular basis (Ständer, 2008). Atopic dermatitis (AD) is a chronically relapsing skin disease highly associated with chronic itch (Hanifin and Rajka, 1980). In AD patients, itch often leads to sleeping problems (Lavery et al., 2016) and is associated with a lower psychological wellbeing (Chrostowska-Plak et al., 2013).

In order to better understand physiological processes of itch, methods to induce itch in experimental settings are needed. Two methods that are often used to induce itch in laboratory settings are the application of cowhage (mucuna pruriens) through rubbing or of histamine through iontophoresis (e.g., Papoiu et al., 2011a). However, also the presentation of certain (audio-) visual stimulus material has repeatedly been shown to induce itch. By now there are several studies, which found that the presentation of itch-related stimuli, like pictures of crawling insects or videos showing other people scratching, can trigger itch and scratch responses in both healthy subjects and patients with chronic itch (Niemeier et al., 2000; Papoiu et al., 2011b; Lloyd et al., 2013; Schut et al., 2014, 2015b). However, so far there are only two studies, which investigated brain activity induced by such itch related stimuli (Holle et al., 2012; Mochizuki et al., 2013). The phenomenon that one also feels itch and starts scratching when one is confronted with itch stimuli has been referred to as contagious itch (CI) (Papoiu et al., 2011b; Schut et al., 2015a). CI is similar to another universal phenomenon called contagious yawning (Platek et al., 2005). Interestingly, in psychophysical studies CI and the subsequent scratching behavior were found to be more profound in patients suffering from chronic itch due to AD than in healthy controls (Papoiu et al., 2011b; Schut et al., 2014): Papoiu et al. (2011b) showed that the simultaneous application of a mock stimulus (saline) and an experimental video (EV) showing people scratching led to a significant increase of itch intensity in AD patients, while it only led to a slight increase in itch perception in healthy controls. In accordance, also Schut et al. (2014) found that AD patients displayed a more profound response to audio-visual itch stimuli compared to healthy controls. The patients reported a higher itch increase and displayed more scratching in response to a video on itch-related stimuli than healthy controls. Thus, it has repeatedly been shown that AD patients are more susceptible to (audio-) visual itch-cues than healthy controls. This finding can in terms of associative learning processes possibly be explained by the fact that an association between itch-related stimuli and itch/scratching has been experienced more often by chronic itch patients than healthy controls.

In order to help AD patients it is thus crucial to find ways to break the sequence of itch and scratching resulting in further inflammation known as the itch-scratch cycle (Yosipovitch and Papoiu, 2008) which occurs during CI. Until now, brain processing of CI has only been investigated in healthy controls (Holle et al., 2012; Mochizuki et al., 2013): In the first study, it was found that the presentation of videos showing other people scratching led to an activation of the anterior insular cortex (aIC), the parietal cortex including the primary somatosensory cortex, and the prefrontal cortex (Holle et al., 2012). In another study, an activation of motor-related areas, e.g., the supplementary motor area (SMA) and basal ganglia as well as of parts of the insular cortex were observed when participants were shown itch- related pictures (Mochizuki et al., 2013). Thus, in healthy participants CI goes along with an activation of brain areas that are also activated during itch provoked by pruritogens (Mochizuki et al., 2014). However, the brain processing of CI has never been investigated in AD patients. The investigation of brain processing in this group of patients is of high interest in order to identify brain regions which could be target regions for non-invasive treatments (Mochizuki et al., 2017).

MATERIALS AND METHODS

Subjects

Eleven participants were enrolled in the study: six female and five male AD-patients (mean age: 32.8 ± 11.8 years). All had to have an itch rating of at least 4 out of 10 in a visual analog scale during the past 2 weeks prior to study initiation. All participants were right handed, neurologically healthy and in general good health with no other skin disease, disease state, or physical condition which would impair the evaluation of their itch intensity or which would increase their health risk by study participation. Moreover, all patients were susceptible to the visual itch cues used in our study. In order to verify this, they were presented two videos during a screening visit. Only patients reporting an increase in itch intensity of at least 3 on a visual analog scale ranging from 0 to 10 (0: no itch; 10: worst imaginable itch) due to the EV in comparison to the control video (CV) were included in the study (see also "itch induction"). This inclusion criterion was applied in order to ascertain that we would be able to identify brain regions activated during CI in all participants. Thirteen out of 19 screened subjects, reported an itch increase of at least 3 on a VAS from 0 to 10. Two of the eligible patients did not undergo the fMRI tests due to technical issues and therefore 11 atopics completed the study.

Ethics Statement

All subjects signed an informed consent before study participation and were free to withdraw from the study at any time. Before the beginning of the study, the study protocol had been approved by the Institutional Review Board (IRB) of the Temple University School of Medicine, Philadelphia, PA, United States and was found to conform to the guidelines of the World Health Organization (Declaration of Helsinki).

Design and Procedure

While lying in the scanner, participants were presented with two videos, one of which induced itch (EV) and a second one, which was not itch-inducing (CV). The order of video presentation varied between participants. Before each video presentation, the patients were instructed to keep their head still and to relax as much as possible during the video presentation. Participants were told that they were not allowed to scratch in the scanner. After each video presentation, they were asked to report their itch ratings using a response button. In between the videos, there was a 30 min wash-out period. This was in particular important in order to ensure that the itch due to the EV had fully disappeared during the presentation of the CV. During the wash-out period, all participants remained inside the scanner and were told that they were not allowed to fall asleep.

The same procedure of itch induction was repeated outside the scanner after the MRI measurements. This was done in order to be able to also measure the scratching behavior outside the scanner during CI.

Itch Induction

Itch was induced by a video showing people scratching (EV). A video showing the same people sitting idle was used as a CV. Both videos lasted 5 min and 50 s. The videos consisted of ten sequences, which lasted 30 s each. In addition, in between these sequences a pause of 5 s was included. The 30 s sequences each showed one person, who either scratched the right forearm (EV) or sat idle looking straightforward (CV). The persons appeared in the same order in both videos. Two of the shown persons were female and one was male. These videos were validated in a previous study, in which it was shown that they led to an increase in itch/scratching in AD-patients and healthy controls (Papoiu et al., 2011b).

Psychophysical Measurements

The average itch intensity that occurred due to the videos was measured by means of a visual analog scale ranging from 0 to 10 (0: no itch, 10: worst itch imaginable) immediately after each video presentation. The patients were asked to answer the following question using a response button in the scanner: "How itchy have you felt during the last video presentation on average?". Moreover, the number of scratch movements and the scratch duration that occurred during the presentations of the videos outside the scanner were video-recorded and subsequently rated by two independent persons not involved in data collection, who did not know the sequence of video presentation. The interrater-reliability was $r \geq 0.90$ for all videos.

MRI Measurement and Data Analysis

Due to the fact that participants in this study continuously viewed the videos for 5:50 min to induce itch, which can induce slow changes of neural activity in the brain, we decided to use arterial spin labeled (ASL)-functional MRI (fMRI) to measure brain activity, because this method is suitable for detecting such slow changes. The scanner that was used was a 3Tesla Verio MR scanner, Siemens, Erlangen, Germany. The Pseudo-Continuous Arterial Spin Labeling (pCASL) pulse consisted of 1520 selective radiofrequency (RF) pulses (Hanning window, B1 average = 1.8 μT, duration = 500 μs, spacing = 500 μs, $G_{average}$ = 1 mT/m, $G_{maximum}/G_{average}$ = 8) with a labeling duration of 1527.6 ms and post-labeling delay (PLD) of 1500 ms. $G_{maximum}$ represents the gradient amplitude during each Hanning pulse. $G_{average}$ represents the average gradient applied between the center of two RF pulses. For the control, the RF phase alternated from 0 to 180°. Identical G waveforms were used for label and control acquisitions. The inversion plane was offset 8 cm from the center of the field-of-view (FOV) in the head–foot direction, so that it was located at the base of the cerebellum to achieve good labeling efficiency. The readout parameters were selected as follows: TR = 4000 ms, echo time (TE) = 12 ms, excitation flip angle = 90°, in-plane resolution = 3.4 mm × 3.4 mm, matrix = 64 × 64, slice thickness = 6 mm, 16 slices with 3 mm gap acquired in ascending order, BW = 2790 Hz/px, FOV = 256 × 256 mm2, phase-encoding direction = anterior–posterior (A–P), total readout time (for all 16 slices) = 700 ms.

We used statistical parametric mapping 8 (SPM8[1]) for analysis of the MRI data. Cerebral blood flow (CBF) image was obtained by processing the MRI data using the published toolbox to create CBF image (ASLtbx[2]). Then, we subtracted the CBF image in the CV condition from that in the EV condition. This subtracted image (i.e., delta-CBF image) was then spatially normalized to MNI template brain and smoothed with a Gaussian kernel (6.4 mm × 6.4 mm × 9 mm) using SPM. In order to detect brain areas that were activated during CI, a one sample t-test was conducted. In addition, we also performed correlation analysis using delta-CBF image and difference in itch intensity between CV and EV (i.e., delta-itch intensity). In this analysis, we investigated brain regions in that activity during EV showed significant correlation with delta-itch intensity. Analysis of co-variance (ANCOVA) was applied in the above statistical tests to minimize global effects (i.e., individual difference in global delta-CBF). Voxel-level threshold for above SPM analyses was set at uncorrected $p < 0.001$. Cluster-level threshold for the analyses was set at greater than 50 for minimizing a risk to detect artifacts as significantly activated areas.

Analysis of Psychophysical Data

The statistical analysis of the psychophysical data was performed using SPSS 22 (IBM, Ehningen, Germany). Paired-samples t-tests were used to determine whether the average itch intensity and scratching significantly differed during the presentation of the EV and CV. The intended level of significance was $p < 0.05$. Means ± SEM are presented in **Figures 1**, **2**.

RESULTS

Itch Induction and Scratching Behavior (Outside of the Scanner)

As shown in **Figure 1**, itch intensity was significantly higher during an itch inducing EV (EV condition) compared to the presentation of the CV (CV condition) [$t(10) = -4.980$; $p = 0.001$]. Frequency and duration of scratching in the EV condition were also significantly increased compared to those in the CV condition (frequency of scratching: [$t(10) = -4.366$; $p = 0.001$]; duration of scratching: [$t(10) = -3.528$; $p = 0.009$]; **Figure 1**). The mean itch intensity during the presentation of the CV was 1.57 ± 1.11, while it was 4.18 ± 2.14 during the presentation of the EV. The mean scratch duration and number of scratch movements during the presentation of the CV was 9.27 ± 7.68 s and 4.5 ± 3.35 scratch movements, respectively, while it was 30 ± 19.49 s and 11.95 ± 6.64 scratch movements during the presentation of the EV.

Itch Induction (Inside the Scanner)

Average itch intensity during the presentation of the EV in the scanner also significantly differed from the average itch intensity during the CV [$t(10) = -6{,}410$; $p \leq 0.001$]. The

[1]http://www.fil.ion.ucl.ac.uk/

[2]https://cfn.upenn.edu/~zewang/ASLtbx.php

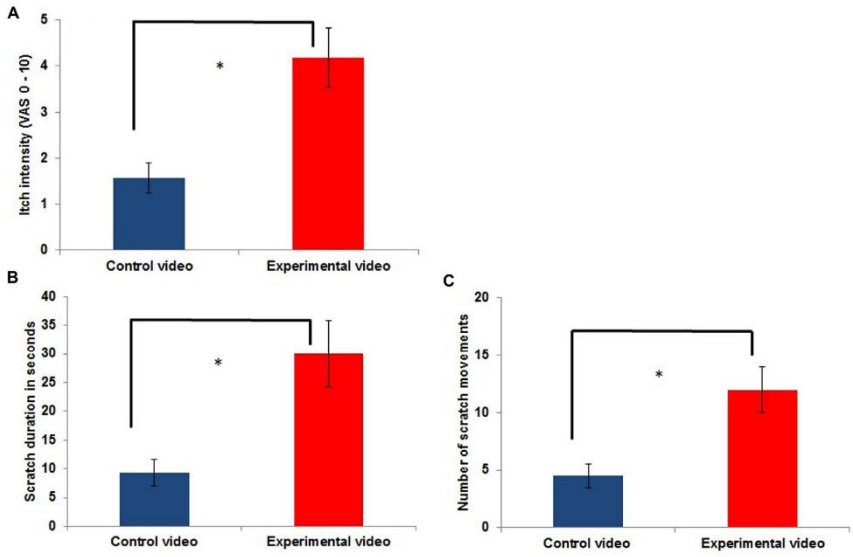

FIGURE 1 | Itch intensity **(A)** and scratching **(B,C)** *outside the scanner* during the control condition [presentation of a control video (CV)] compared to itch during the experimental condition [contagious itch (CI) condition: presentation of a video showing other people scratching; experimental video (EV); $n = 11$; $^*p < 0.05$].

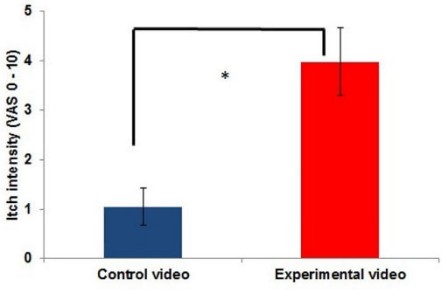

FIGURE 2 | Itch intensity *inside the scanner* during the control condition (presentation of a CV) compared to itch during the experimental condition (CI condition: presentation of a video showing other people scratching; EV; $n = 11$; $^*p < 0.05$).

mean itch intensity during the presentation of the CV was 1.05 ± 1.29, while it was 3.98 ± 2.27 during the presentation of the EV. Itch intensities during the CV and EV are illustrated in **Figure 2**. All participants reported an itch increase of at least 0.75 inside the scanner [range: 0.75–6; measured with a visual analog scale ranging from 0 (no itch) to 10 (worst itch imaginable)].

Brain Areas Activated under Contagious Itch in Patients with AD

Three brain regions showed a significant activation [uncorrected $p < 0.001$; cluster size (k) > 50] during the presentation of the itch inducing EV in comparison to the baseline condition (presentation of the CV). The presentation of the itch inducing video led to an activation of the SMA, the left ventral striatum and the right OFC (**Figure 3** and **Table 1**).

Correlations between Brain Activation and Psychophysical Data

We also investigated whether the increase in itch intensity was significantly correlated to an increase in brain activity. Here, we found that an increase in average itch intensity due to the EV was by trend positively correlated to an activation of the right temporal cortex, the right posterior opercular cortex (pOPC) and the (pre)cuneus (**Figure 4** and **Table 2**; uncorrected $p < 0.005$; $k > 50$).

DISCUSSION

This study provided an insight into brain processing of CI in AD patients. Knowledge of brain processing of CI in AD may enable to identify target brain regions for treatments which can help AD patients when they are confronted with itch-related

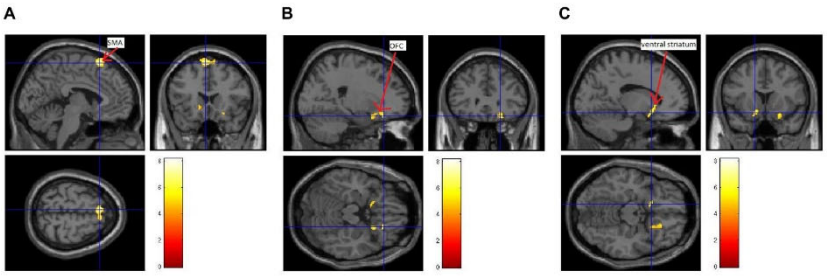

FIGURE 3 | Brain activation during CI in patients with atopic dermatitis. A difference between brain activation during the control condition (presentation of a neutral video) and the presentation of the EV was identified within the supplementary motor area (SMA; **A**), the right orbitofrontal cortex (OFC; **B**) and the left ventral striatum **(C)**.

TABLE 1 | Activation during contagious itch (CI).

	EV > CV			
	MNI coordinate			*Z*-score
Brain regions	***x***	***y***	***z***	
Left SMA	−4	20	64	4.28
Right SMA	8	22	64	3.51
Right OFC	22	30	−18	3.95
	22	14	−18	3.57
Left ventral striatum	−14	14	−14	3.82

SMA, supplementary motor area; OFC, orbitofrontal cortex.

stimuli in daily life. Similar to a previous psychophysiological study (Papoiu et al., 2011b) CI was induced by the presentation of an EV showing other persons scratching. As expected, the presentation of this video led to a significant increase in itch and scratching compared to a CV showing the same persons sitting idly.

We found that activity in the SMA, left ventral striatum, and right OFC significantly increased during the presentation of the EV compared to the presentation of the CV. Thus, these regions seem to be crucial for the experience of CI in AD patients. The SMA, ventral striatum, and OFC are involved in the fronto-striatal circuit. This circuit plays an important role for motivation, craving, motor control and preparation, and decision-making (Fried et al., 1991; Krakauer and Ghez, 2000; Smolke et al., 2006; Plassmann et al., 2010; Harsay et al., 2011). In itch perception in particular, this circuit is considered to be associated with the desire to scratch (Mochizuki and Kakigi, 2015). Interestingly, the activation of this circuit was not observed in a previous fMRI study that used a very similar design as ours to investigate brain processing of CI in *healthy subjects* (Holle et al., 2012). A possible explanation for the differences between the two studies is that the fronto-striatal circuit responds excessively to visual itch-related stimuli in AD-patients, which in the following facilitates itch induction and scratching in these patients. This possibility is supported by previous brain imaging studies which found an over-activity in the SMA and the basal ganglia during itch or scratching in chronic itch patients compared to healthy controls (Schneider et al., 2008; Ishiuji et al., 2009; Mochizuki et al., 2015). Therefore, in our point of view, this circuit might be a reasonable target region for non-invasive treatments in AD patients to help them to prevent scratching in itch inducing situations. Interventions that could have an antipruritic effect when being confronted with itch-related stimuli have recently been outlined (Mochizuki et al., 2017): We described that repetitive Transcranial Magnetic Stimulation (rTMS) and transcranial Direct Current Stimulation (tDCS) could be beneficial for patients suffering from chronic itch. Indeed, it has already been shown that tDCS had positive effects in a patient with chronic itch due to neuropathy (Knotkova et al., 2013). In addition, psychological interventions already shown to be effective to lower baseline itch in AD patients (Evers et al., 2009; Bae et al., 2012) might also affect the activity of the fronto-striatal network during CI. We believe that cognitive behavioral therapies including relaxation- and/or habit reversal trainings as well as cognitive restructuring have the potential to alter the patients' attitude toward visual itch cues, which might then go along with a lower motivation to scratch resulting in a lower brain activity in the fronto-striatal circuit when being confronted with itch-related stimuli. Randomized controlled trials including fMRI measurements before and after treatment are thus needed to prove the effects of different non-invasive interventions on brain activity during the presentation of visual itch cues.

Another interesting finding was that visually induced itch was by trend positively associated with activity in the (pre-) cuneus, pOPC and the temporal cortex. The precuneus and temporal cortex are brain areas that play a role in (episodic) memory retrieval (Cavanna and Trimble, 2006; Palombo et al., 2016). It is possible that seeing somebody else scratching activates the patients' memories regarding their own experiences with itch-related stimuli, which might then affect the pOPC as a key region of somatosensory processing. It has been demonstrated that spontaneous activation or electrical stimulation of this region can generate pain via the activation of brain network associated

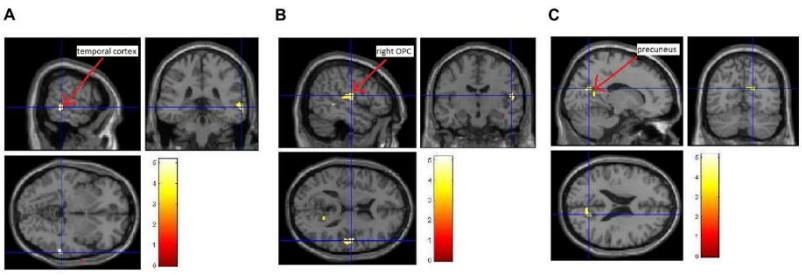

FIGURE 4 | Correlation between induced itch and induced brain activity. We observed a trend of positive correlation (uncorrected $p < 0.005$; $k > 50$) between the increase in itch intensity and the increase in brain activity of the temporal cortex **(A)**, the right pOPC **(B)**, and the (pre-) cuneus **(C)**.

TABLE 2 | Correlation between induced itch and the activation of brain regions during CI.

	EV > CV			
	MNI coordinate			*Z*-score
Brain regions	***x***	***y***	***z***	
Temporal cortex	64	−36	−4	3.34
Right pOPC	52	−12	14	3.26
	56	−20	12	3.12
(Pre-)Cuneus	16	−64	22	2.84
	16	−54	12	2.81
	8	−68	22	2.70

with pain (Garcia-Larrea, 2012). Considering similarity of brain network between itch and pain (Ständer and Schmelz, 2006; Yosipovitch et al., 2007), it may be possible that memory retrieval depicted by the activation of the precuneus and temporal cortex activates the pOPC, which induces the significant activation of the fronto-striatal circuit in AD-patients.

Moreover, we would like to stress the role of the precuneus for the experience of itch in *AD patients*. This region has been shown to be involved in the processing of itch transmitted by histaminergic and non-histaminergic pathways (Mochizuki et al., 2009; Papoiu et al., 2012), and to be significantly more activated during itch processing in AD patients compared to healthy controls (Ishiuji et al., 2009). Interestingly, this region has been shown to be not involved in pain processing (Apkarian et al., 2005; Yosipovitch and Mochizuki, 2015). Instead, an activation of the precuneus has been linked to empathy (Farrow et al., 2001). We speculate that in the context of CI an activation of the precuneus could be seen as a sign of a high ability of taking the perspective of others. In future studies it would therefore be interesting to test the hypothesis that very empathetic patients show more intense itch and more scratching behavior during CI and that this more profound response goes along with more activation in the precuneus.

There are some limitations to this study, which need to be addressed. First, one might argue that we cannot distinguish between whether the activation of the brain regions that we found is "CI specific" or rather a response to the observation of actions, because videos also differed in that way that people in the EV moved while they were sitting idly in the CV. However, previous brain imaging studies investigating the cerebral processing of action observation have not observed the activation of the regions that we observed. Instead they have commonly observed the activation of other brain regions such as the dorsolateral prefrontal cortex (DLPFC), premotor cortex (PM), and parietal cortex (Buccino et al., 2004a,b; Calvo-Merino et al., 2006; Iacoboni and Dapretto, 2006). The results of these previous studies in combination with our profound increase in itch/scratching seen in the psychophysical data strengthen our confidence that we actually measured CI related brain activity and not brain activity that occurred due to the observation of actions. As a second limitation, our sample size was rather small with $n = 11$ patients and data of a healthy control group are not included in this study. However, the purpose of the present study was to investigate which parts of the brain are activated in patients with chronic itch while they view scratching behavior in others, and not to identify brain regions responsible for the robustness of CI seen in AD patients in comparison to healthy subjects. Therefore, our study should be regarded as a pilot study. A further fMRI study including a larger sample of patients and healthy participants could narrow down candidate brain regions responsible for the augmented CI seen in AD patients. This may finally lead to the identification of target regions for non-invasive treatments of CI in patients with AD (Mochizuki et al., 2017). Third, also confounding factors like the patients' personality and the expectations regarding the upcoming itch stimuli that have recently been shown to be associated with the patients' response to audiovisual itch cues (Schut et al., 2014, 2016) should be taken into consideration in future studies with larger sample sizes.

Despite these limitations, this study was the first pilot study to elucidate mechanisms of CI in the brain of patients with atopic eczema suffering from chronic itch. Future studies that would

examine whether similar mechanisms occur in other types of chronic itch would be of major interest.

AUTHOR CONTRIBUTIONS

CS overall conceptualization of the study, data collection, statistical analysis, participation in analyses of the MRI data, and writing the paper. HM contributions to the conceptual design, statistical analysis, supervision of data collection, analyses of the MRI data, and writing the paper. SG analysis of scratching behavior, data input. AL analysis of scratching behavior. CC supervision of MRI data collection, participation in analyses of the MRI data, discussion of results. FM supervision of MRI data collection, participation in analyses of the MRI data, discussion of results. UG participation in overall conceptualization of the study. JK participation in overall conceptualization of the study, participation in statistical analysis of psychophysical data, discussion of results. GY participation in overall conceptualization of the study, participation in recruitment of participants, discussion of results, and writing the paper. All authors read and approved the manuscript.

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7.5 Publikation 3

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INVESTIGATIVE REPORT

Personality Traits, Depression and Itch in Patients with Atopic Dermatitis in an Experimental Setting: A Regression Analysis

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It is known that itch is associated with psychological variables, but it is not known whether personality characteristics, depression or anxiety are predictors of experimentally induced itch in patients with atopic dermatitis (AD). In this study itch was induced in 27 patients with AD and 28 healthy controls by the presentation of an experimental video on crawling insects and skin diseases. Itch intensity was measured by self-ratings and by observing the number of scratch movements. Itch increase was determined by subtracting itch intensity induced by the experimental video from itch intensity induced by a control video. Psychological variables were assessed using validated questionnaires. In patients with AD, depression was a significant predictor of self-rated induced itch (corrected R^2=0.175); while agreeableness and public self-consciousness were significant predictors of induced scratching (corrected R^2=0.534). In healthy controls no associations were found. These results imply that a special group of patients with AD might benefit from certain psychological interventions. ***Key words: atopic dermatitis; psychodermatology; personality characteristics; depression; anxiety.***

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Itch, an unpleasant sensation that evokes the desire to scratch (1), is a widespread phenomenon in the general population (2–5) and especially in patients with skin diseases (6–8). It is a major symptom, e.g. in patients with atopic dermatitis (AD) (6), urticaria (7) and psoriasis (8). Itch can have many causes, and there are several physiological reactions that are associated with the occurrence of itch (9–12), but itch is also associated with psychological variables such as the emotional state of the subjects (13–15). In a recently published study it was, for example, shown that negative emotions, induced by the presentation of films, increased itch intensity in healthy women (13). In another study, state anger was associated with itch intensity in patients with chronic urticaria, while depression was associated with itch intensity in patients with psoriasis (14). Moreover, in patients with psoriasis scratching as well as worrying was related to self-rated itch increase 4 weeks later, but only in times of high daily stressors (15).

In addition, personality, the way individuals think, behave and feel (16), is associated with itch (17, 18). Individuals differ in the degree of personality traits, such as extraversion, neuroticism (emotional lability), conscientiousness, openness to experience and agreeableness (16). In addition, one aspect of self-consciousness was shown to be associated with itch intensity: the more subjects focused on their bodily sensations, the greater was the experimentally induced itch intensity they experienced (17). Furthermore, some older studies found a certain personality structure in patients with the highly itchy skin disease atopic dermatitis: patients with AD were described as more neurotic, hostile, anxious and depressive than healthy controls, and as having more problems dealing with their anger and hostility (19–22). Moreover, a small correlation was found between itch intensity and neuroticism scores in patients with AD and psoriasis (18).

Findings like these, together with the fact that itch intensity cannot always be completely explained by the severity of the skin disease, led to the postulation of a biopsychosocial model of itch (23). This model assumes that internal factors (e.g. personality characteristics) together with external factors (e.g. stressors) lead to certain cognitions, social reactions and/or behaviours, which then might increase or decrease physiological reactions. In this model these physiological reactions lead to itch (23). The purpose of this study was to analyse one part of this biopsychosocial model of itch, namely the relationship between internal factors of a person and induced itch. Concerning internal factors, we were especially interested in personality characteristics, depression and anxiety, because a relationship between these variables and the occurrence of the itchy skin disease AD has already been shown. The objective of this study was to investigate the association between these psychological variables and *induced itch* in this patient group. To our knowledge, this has not been done previously. In order to induce itch we used the method of mental itch induction

(which comprises the presentation of certain audiovisual material, also see itch induction), which was quite similar to the method used in another, recently published study (24). The advantage of this method is that, in contrast to other methods of itch induction (e.g. the histamine-prick test), it does not need direct manipulation of the skin. This study investigated the research question: Are personality characteristics, depression and anxiety predictors of induced itch in patients with AD?

MATERIALS AND METHODS

Participants

Patients with AD ($n=30$) and healthy controls ($n=30$) were recruited through written announcements in a weekly newspaper, or directly addressed at the campus of the University of Gießen, Germany. Patients with AD were additionally recruited at the dermatology department of the university hospital and at surgeries of local dermatologists. Subjects received a 15 € expense allowance for participation in the study.

Through a first telephone interview exclusion and inclusion criteria were determined. Patients were included if they had clinically diagnosed AD. They were instructed not to use any topical itch reducing medication at least 24 h prior to the investigation. Exclusion criteria in patients with AD were: any other somatic and/or psychiatric disease as well as oral medications 4 weeks prior to the study. Healthy controls were excluded if they reported any somatic and/or psychiatric disease, or family history of atopic diseases. The group of AD patients and the group of healthy controls were stratified according to age and gender.

Design overview

All participants came in groups of 3–4 persons to our observation laboratory assuming to evaluate teaching material concerning the skin and its function. Participants were separated by divider walls in order not to influence each other and were then shown 2 videos in counterbalanced order (also see itch induction, below). In this cross-over study, participants were randomized to the order of presentation of the videos. Immediately after each video a "wash-out" period of 30 min followed, during which the participants rated their actual itch intensity and completed questionnaires to measure personality characteristics (see predictor variables). At the end of the appointment, subjects were informed about the true intention of the study (also see ethics). Table I presents the time-line of the study.

Itch induction

Itch was induced by the method of mental itch induction. This method is based on the idea that because of classical conditioning processes (22), certain audiovisual stimulus material is able to induce itch. An experimental video (EV) on "Itch – what is behind it?" was used to induce itch, while a video on "Skin – the communication organ" served as a control video (CV). Pictures included in the EV were selected by 2 itch researchers (UG, JK) according to the stimulus material that was used in a former field-study in which a slide-supported lecture that included pictures of skin diseases and crawling insects induced itch (25). Thus, our EV also included pictures of fleas, flea-bites on a human body, mites under the skin, lice and hair that is affected by lice as well as a body of a girl with AD and the body of a person with contact eczema. In addition, one picture showing people scratching and one showing monkeys lousing each other were included.

The CV contained pictures showing, for example, two touching hands, a kissing or hugging couple, a man lying in a bath, a mother carrying her baby, or two children with the upper part of their bodies naked sitting next to each other on a swing. In the videos, a speaker (UG) talked in the background while pictures were presented as a slideshow. The videos lasted approximately 11 min each and contained 15 pictures.

Assessment of increase in itch

Self-rated itch intensity was determined using a visual analogue scale (VAS) ranging from 0 to 10 (0: no itch; 10: unbearable itch). The criterion variable self-rated induced itch was determined by subtracting self-rated itch intensity measured immediately after the presentation of the EV from self-rated itch intensity measured immediately after the presentation of the CV.

The number of scratch movements (observed itch) was assessed during the whole presentation of the videos. It was rated by 2 independent persons. Here, the criterion variable induced scratching was determined by subtracting the number of scratch movements during the presentation of the EV from the number of scratch movements during the presentation of the CV. To secure that the raters only counted scratch movements and not spontaneous touching, they were instructed and calibrated by a dermatologist (UG) before the beginning of the study. Scratching was defined as any movement that included rubbing and was distinguished from touching, which was defined as any rapid contact of an extremity including movement, but not rubbing. The inter-rater reliability for the EV was $r=0.99$ ($p\leq0.001$), and for the CV $r=0.93$ ($p\leq0.001$).

Assessment of predictor variables

Personality characteristics, depression and anxiety were taken into consideration as predictors of induced itch. The following questionnaires were used to measure personality characteristics, depression and anxiety:

- The Neo Five-Factor Inventory (NEO-FFI) includes 60 items and measures 5 personality traits: neuroticism, extraversion, openness to experience, agreeableness and conscientiousness (26).
- The Hospital Anxiety and Depression Scale (HADS), a 14-item questionnaire, measures anxiety and depression (27).
- The Self-Consciousness Scale (SCS) includes 27 items and measures private as well as public self-consciousness (28).

Ethics

The study design was approved by the local ethics committee, which found that the study protocol conformed to the Declaration of Helsinki. All participants provided their written, informed consent to the study and were free to withdraw from the

Table I. *Timeline of the study. Videos 1 and 2 were presented in counterbalanced order*

Actions	0–10 min Introduction	10–20 min Video 1	20–50 min Wash-out Period 1	50–60 min Video 2	60–90 min Wash-out Period 2	90–100 min Debriefing
Measurements		Number of scratch movements	Subjective itch intensity + personality characteristics	Number of scratch movements	Subjective itch intensity + anxiety, depression and self-consciousness	

study at any time. At the beginning of the study, participants were told a cover story intended to make them believe, that they took part in a study that aimed to measure the quality of teaching material. The title of the study was: "Evaluation of video-material concerning different functions of our skin – a comparison of patients with AD and healthy controls." At the end of the investigation all participants were debriefed and informed about the true intention of the study.

Statistical analysis

To be able to detect changes in itch intensity due to the different video presentations we aimed to recruit a sample size of $n=54$ to achieve a statistical power of 95% with a given significance level of 5% for medium effect sizes ($f=0.25$). To allow for possible missing data and outlier scores, we examined a total of 60 subjects (30 in each group) to secure a final sample size of $n=54$. The final sample size was 55, because we had to exclude 5 participants (3 patients with AD and 2 controls with healthy skin) who reported having chronic diseases (see sample characteristics). The identification of predictors of itch increase in the 2 subsamples followed an exploratory approach.

Statistical analyses were performed using SPSS 20. Kolmogorof-Smirnov Goodness-of-Fit Test indicated no violation of the normal distribution assumption for any predictor or criterion variable. To compare patients with AD and healthy controls regarding sociodemographic data and personality characteristics, *t*-tests for independent samples or χ^2-tests were calculated. To analyse whether patients with AD and healthy controls differed concerning self-rated or observed itch intensity after/during the presentation of the EV, 1-way analyses of covariance with factor group (AD vs. healthy controls) and the respective baseline measure as covariate (self-rated or observed itch intensity after/during the presentation of the CV) were conducted. To identify predictors of itch increase in the group of patients with AD or controls with healthy skin, a stepwise forward linear regression analysis was conducted for each group: Personality factors, anxiety and depression, as well as private and public self-consciousness were used as predictor variables, while the difference between CV and EV concerning the number of scratch movements or itch intensity was used as the criterion variable.

RESULTS

Sample characteristics

A total of 30 subjects with clinically diagnosed AD and 30 healthy controls were examined. Despite the inclusion of subjects after the telephone interview (due to negotiation of exclusion criteria), 5 subjects had to be excluded after participation in the study. Three patients with AD had to be excluded because they reported having asthma, allergies or idiopathic thrombocytopenic purpura in addition to their skin disease. Similarly, 2 participants in the control group had to be excluded because of asthma or diabetes mellitus. Thus, the group of controls with healthy skin comprised 18 female and 10 male subjects; 12 patients with AD were male and 15 were female. Groups did not differ concerning age: the mean ± SD age in the group of healthy subjects was 23.3 ± 2.1 and 23.6 ± 3.7 in the group of patients with AD. Moreover, *t*-tests indicated no group difference concerning conscientiousness [t (53) = 0.757; $p=0.453$], openness to experience [t (53) = 0.610; $p=0.545$], anxiety [t (53) = –1.193; $p=0.238$], private [t (53) = –1.043; $p=0.302$] or public self-consciousness [t (53) = –0.848; $p=0.400$]. Significant differences were observed for neuroticism [t (53) = –2.491; $p=0.016$], extraversion [t (53) = 2.613; $p=0.012$], depression [t (53) = –2.961; $p=0.005$] and agreeableness [t (53) = 2.142; $p=0.037$]. Patients with AD were more neurotic, less extraverted, less agreeable and more depressed than controls with healthy skin. The means and SDs concerning the personality characteristics, anxiety and depression are presented for both groups separately in Table II.

Manipulation check "itch induction"

Self-rated itch intensity measured after watching the EV was rated as significantly higher than itch intensity after watching the CV [F (1/52) = 8.025; $p=0.007$; $\eta^2=0.134$]. The mean ± SD of itch intensity immediately after the presentation of the CV was 1.91 ± 2.96, while it was 4.71 ± 3.64 immediately after the EV. Moreover, the number of scratch movements was significantly higher while watching the EV compared with watching the CV [F (1/52) = 19.492; $p \leq 0.001$; $\eta^2=0.273$]. The mean ± SD of the number of scratch movements increased from 3.22 ± 3.73 during the presentation of the CV to 9.28 ± 8.71 during the presentation of the EV.

Self-rated itch intensity increased in 21 patients with AD, in 3 it decreased and in 3 it remained the same. In patients with AD, the mean ± SD of itch intensity immediately after the presentation of the CV was 2.56 ± 3.46, while it was 5.89 ± 3.51 immediately after the presentation of the EV. In 20 healthy controls the self-rated itch intensity increased, while in 7 the itch intensity remained the same. Itch intensity decreased in only one healthy person. In healthy controls the mean ± SD of itch intensity immediately after the presentation of the CV was 1.29 ± 2.28, while it was 3.57 ± 3.45

Table II. *Population characteristics concerning the predictor variables*

Predictor variables	AD patients ($n=27$) Mean ± SD (range)	Controls ($n=28$) Mean ± SD (range)
Depression	5.30 ± 3.69 (0–12)	2.75 ± 2.62 (0–11)
Anxiety	7.33 ± 3.97 (0–15)	6.21 ± 2.92 (1–12)
Private self-consciousness	3.63 ± 0.56 (2.38–4.77)	3.48 ± 0.50 (2.38–4.54)
Public self-consciousness	3.53 ± 0.55 (2.21–4.57)	3.41 ± 0.51 (2.57–4.57)
Neuroticism	2.02 ± 0.66 (0.83–3.67)	1.59 ± 0.61 (0.50–2.83)
Extraversion	2.26 + 0.55 (0.67–3.50)	2.64 + 0.53 (1.58–3.67)
Openness to experience	2.70 ± 0.60 (1.50–3.75)	2.79 ± 0.47 (1.75–3.67)
Agreeableness	2.53 ± 0.57 (1.50–3.58)	2.84 ± 0.50 (1.75–3.58)
Conscientiousness	2.47 ± 0.71 (0.58–3.25)	2.60 ± 0.61 (1.50–3.50)

immediately after the presentation of the EV. Results of the analysis of covariance (ANCOVA) (self-rated itch intensity after the CV as covariate) indicated that, by trend, patients with AD reported a higher itch intensity than healthy controls after the presentation of the EV [$F(1/52) = 3.528$; $p = 0.066$; $\eta^2 = 0.064$].

In 22 patients with AD the number of scratch movements increased, in 4 it was unchanged, and only one patient with AD scratched less during the presentation of the EV than during the presentation of the CV. In the patient-group, the mean ± SD of the number of scratch-movements during the presentation of the CV was 3.28 ± 3.35, while it was 12.7 ± 10.36 during the presentation of the EV. In 19 healthy controls the number of scratch-movements increased, while it was unchanged in 4 participants. Five controls scratched less often during the presentation of the EV than during the presentation of the CV. In the group of healthy participants, the mean ± SD of the number of scratch movements during the presentation of the CV was 3.16 ± 4.12, while it was 5.98 ± 5.05 during the presentation of the EV. Results of the ANCOVA (observed number of scratch movements while watching the CV as covariate) indicated that patients with AD showed significantly more scratch movements than healthy controls during the presentation of the EV [$F(1/52) = 15.385$; $p \leq 0.001$; $\eta^2 = 0.228$]. The increase in scratch movements was not significantly related to the increase in itch intensity, neither in the group of patients with AD ($r = 0.278$; $p = 0.161$) nor in the group of healthy controls ($r = 0.072$; $p = 0.714$).

Fig. 1. illustrates the itch intensity immediately after the presentation of the videos and the number of scratch movements during the presentation of the videos in patients with AD and healthy controls.

Personality characteristics, depression and anxiety as predictors of itch increase in patients with atopic dermatitis

An initial regression analysis revealed that depression was a significant predictor of induced itch in patients with AD. Of the variance of the increase in itch intensity from CV to EV, 17.5% (corrected $R^2 = 0.175$) could be predicted by this psychological variable. Patients with high scores on the depression scale (HADS-D) reported higher increases in itch intensity than patients with low scores on the depression scale. The results of the regression analysis are shown in Fig. S1[1]. In healthy controls, the increase in self-rated itch intensity could not be predicted by personality characteristics, depression or anxiety.

A second linear regression analysis revealed that 53.4% (corrected $R^2 = 0.534$) of the increase in the number of scratch movements from CV to EV could be predicted by the combination of public self-consciousness and agreeableness in patients with AD. Patients who scored high on public self-consciousness and low on agreeableness showed a higher increase concerning the number of scratch movements than patients with the opposite scores in these scales. The results of this regression analysis are also shown in Fig. S1[1]. In healthy controls, the observed increase in the number of scratch movements could not be predicted by personality characteristics, depression or anxiety.

DISCUSSION

In line with the results of another study (24) we were able to show that itch can be induced not only by direct skin-manipulation, but also by the presentation of certain video material. Furthermore, corresponding to the results of the earlier study (24), in the present study AD patients were also more sensitive to itch-inducing material than healthy controls.

The important novelty of this study is that, in addition, personality characteristics and depression could be identified as predictors of experimentally induced itch in patients with AD. Patients who scored highly on depression reported higher induced itch than patients, who stated not being depressive. This interesting result is in accordance with the results of other studies (14, 29, 30), in which associations between itch intensity and

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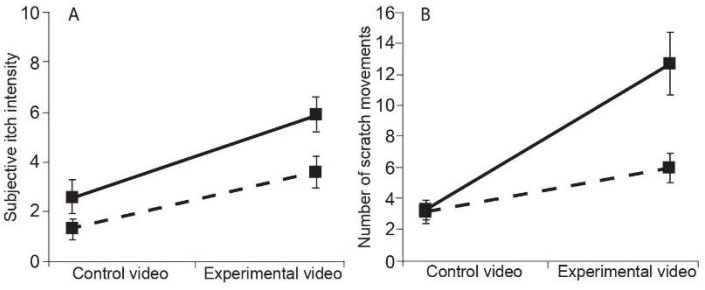

Fig. 1. Mental itch induction. Subjective itch intensity (A) immediately after the presentation of the videos and the number of scratch movements (B) during the presentation of the videos in patients with atopic dermatitis (*continuous line*; $n = 27$) and healthy controls (*dotted line*; $n = 28$).

depression were shown for skin patients. The difference between the results of these studies and our study is that itch was not experimentally induced in the other studies. Instead, itch was measured in a point-wise measurement using self-reports. Thus, the other studies do not allow a statement on whether *induced itch* is associated with depression, while the present study provides preliminary evidence for this association.

Furthermore, in patients with AD, more than 50% of the variance in induced scratch movements could be predicted by agreeableness and public self-consciousness: patients who reported not being very agreeable and at the same time scored high on public self-consciousness showed a higher increase in the number of scratch movements than agreeable patients who did not care much about what others thought about them. This finding widens the result of another study, in which attention to bodily sensations was positively associated with experimentally induced itch (17). In the present study it was not awareness of oneself, but rather awareness of others nearby, that was of importance regarding induced itch. One explanation for this finding could be that patients with AD, similarly to patients with psoriasis, feel stigmatized because of their skin disease (31), and therefore develop feelings of being critically observed or excluded by others. This explanation would also fit with the finding that patients with AD feel more uncertain and determined by others and have a lower self-esteem than healthy controls (32). In addition, low agreeableness was associated with an increase in scratch movements. Persons with low scores on this personality scale are described as aggressive and rude (16). In earlier studies patients with AD were shown to anger more quickly than healthy controls, but at the same time were less able to express and cope with their anger (21). The present study is the first to show that this personality trait in combination with high public self-consciousness is also associated with induced itch in this patient group.

The results of this study not only support the view that psychological concepts, such as depression and personality characteristics, are associated with induced itch in AD, but also emphasize that psychological interventions could be a helpful addition in the treatment of this patient group. Positive effects of psychological interventions have already been shown for patients with AD (33–38). This study even goes a step further, because it suggests that a special group of patients with AD might benefit from certain psychological interventions: patients showing a psychological phenotype that comprises high depression, low agreeableness and high public self-consciousness would probably benefit from psychological interventions, such as cognitive restructuring, anger management and self-assertiveness training, because these interventions might be able to modulate the extent of the personality characteristics that are associated with induced itch. As a consequence, the appearance of itch-inducing stimuli might not automatically have to lead to scratching behaviour, which is associated with a worsening of inflammation (itch-scratch-cycle; 39).

There are also some limitations to the study. First, because we only included patients with AD without any other somatic and/or psychiatric disease (including other atopic diseases) we cannot generalize the results of the present study to other populations of patients with AD, e.g. patients with more than one atopic disease. Since patients with AD often have a combination of atopic diseases (40) and not only AD, a possible way of minimizing this selection bias would be to include patients with more than one atopic disease in future studies and to investigate whether the same personality characteristics are associated with induced itch in these patients. Secondly, at this point we are not able to determine whether our itch-inducing video also caused stress, because we did not assess stress-parameters such as cortisol after presentation of the EV. For future studies it would therefore be interesting to compare the possibly evoked stress reaction by the video with a stress reaction induced by a validated laboratory stressor (e.g. after using a public-speaking paradigm) in order to gain an impression of whether stress can be considered a mediator for itch induction. A third limitation lies in the fact that we did not consider the severity of AD as a predictor of itch increase, because we did not assess it. In future studies it would be valuable to assess the severity of the skin disease (in patients with AD, e.g. by means of the SCORAD (SCORing Atopic Dermatitis) (41) or POSCORAD (Patient-Oriented SCORAD) (42)) to be able to include it in the regression analysis as a possible predictor.

In conclusion, this study shows that a considerable amount of the alteration in induced itch in patients with AD can be predicted by personality characteristics and depression. If these results can be replicated in further studies, this finding may enable a first approach to identify patient groups who might especially benefit from certain psychological interventions (e.g. anger management).

The authors declare no conflicts of interest.

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7.6 Publikation 4

Schut C[+*], Reinisch K[+], Classen A, Andres S, Gieler U, Kupfer J. Agreeableness as Predictor of Induced Scratching in Patients with Atopic Dermatitis: A Replication Study. *Acta Dermato Venereologica* 2018;98;32-37; doi: 10.2340/00015555-2767; + geteilte Erstautorenschaft; * korrespondierende Autorin;

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INVESTIGATIVE REPORT

Agreeableness as Predictor of Induced Scratching in Patients with Atopic Dermatitis: A Replication Study

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In patients with atopic dermatitis agreeableness and public self-consciousness have previously been shown to be significant predictors of induced scratching, while depression was significantly related to induced itch. This study aimed to replicate these findings. Itch and scratching were induced by videos of crawling insects or skin diseases. Induced itch was measured using a visual analogue scale. Scratching behavior was evaluated by two raters. Psychological variables were assessed using validated questionnaires. Induced scratching could be predicted significantly by agreeableness (corrected $R^2 = 15.5\%$ or 38% after exclusion of one outlier): Patients scoring low on agreeableness showed a higher increase in scratch movements than patients scoring high on this scale. No associations between induced scratching/itch and public self-consciousness/depression were found. One clinical implication that arises from this study could be to offer patients scoring low on agreeableness certain psychological interventions.

Key words: atopic dermatitis; itch; scratching; personality; agreeableness; itch induction.

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Atopic dermatitis (AD) is a chronic inflammatory skin disease which is characterized by lichenification at certain sites of the body and (other) atopic diseases (asthma bronchiale, rhinitis allergica or AD) in the patient and/or his/her family (1). One of the biggest stressors of this disease is the intense itch which bothers AD patients, especially in the evening and at night (2, 3). In order to decrease itch, patients scratch, which is associated with immunological reactions and a worsening of inflammation (4). Almost every AD patient experiences his/her itch as annoying and unpleasant (3). The itch intensity during a usual itching episode is evaluated as very intense in this patient group (8.3 out of 10 points). Furthermore, itch occurs in 91.4% of the patients at least once a day (3). Many AD patients experience heat sensations and pain in combination with their itch (3, 5).

In some older studies, AD patients were shown to have a certain personality structure which was characterized by high neuroticism scores, hostility and the inability to cope with anger (6, 7). Furthermore, patients with AD were found to be more anxious and depressive than healthy controls (6–10) and described themselves as lower in self-efficacy than healthy controls (8). Even though these relationships could be found, Buske-Kirschbaum et al. (11) posit that one should be rather cautious in relating a certain personality profile to the occurrence of AD, because study results are diverse and not every study found a certain personality structure in patients with AD (11). However, personality characteristics and depression seem to be related to the *intensity of itch* in this patient group (12–14). One study showed that neuroticism was positively associated with the intensity of itch in patients with AD and psoriasis (13). In another study, a positive correlation between self-rated depression and itch intensity was found in AD (12). In addition, being more focused on bodily sensations was linked to the intensity of itch in this patient group (14). Even though the correlations in these cited studies were rather low, we were surprised by the results of a study which we published 3 years ago (15). In this study, we investigated the relationship between *induced* itch and *personality* in AD. We found that *induced* itch and scratching in AD patients were strongly related to certain personality characteristics. Induced scratching could be predicted by public self-consciousness and low agreeableness to a very high degree: Patients who report being very concerned about what other people think about them and at the same time describe themselves as rather rude or aggressive and not very agreeable, displayed more induced scratching than patients with the opposite psychological phenotype (corrected $R^2 = 0.534$). Furthermore, AD patients scoring high on depression reported a higher itch increase than patients who stated they were not very depressive (corrected $R^2 = 0.175$). In contrast, these associations were not found in healthy controls (15).

Even though the results of this previous study (15) were interesting, we believe that the findings need to be replicated in a first step in order to draw clinical implications from them in a second step. In a recently published study on the reproducibility of findings in the field of psychology, it has been outlined that 97% of the original articles investigated reported significant results, whereas not even half of the studies aiming to replicate the significant results were able to do so (16). Thus, many published data seem to report incidental findings, which do not justify treatment modifications. From our

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point of view, replication studies are highly desirable in order to justify clinical implications. In clinical settings, false positive results could lead to the application of non-effective treatments, which would then result in unnecessary time commitment of patients and those working in the field of dermatology. In our case it is possible that time-consuming psychological treatments would lead to frustration not only in the patients but also in staff working in the field of psychodermatology should their effects on itch and scratching be rather low. Moreover, unnecessary costs would also result from these time-consuming treatments, meaning a high financial burden for the health system. Therefore, the goal of this study was to replicate the findings of our former study using again participants with AD in comparison to healthy controls. We aimed to answer the following research question: Can agreeableness, self-consciousness and depression again be shown to predict induced itch or scratching in patients with AD? Thus, this study was carried out in order to be able to draw clinical implications from it in a second step in the event that the results of the former study could be replicated.

MATERIALS AND METHODS

Ethics statement

The study was approved by the local Ethics Committee of the Justus-Liebig-University of Giessen, Germany. All participants provided written informed consent and were free to withdraw from the study at any time.

Participants

Twenty-three AD patients and 23 healthy skin controls were included in the study (see Fig. S1[1]). Participants were recruited through announcements in a weekly newspaper and at the campus of the Justus-Liebig-University as well as at the Dermatology Department of the University Clinic of Giessen. AD patients were included if they suffered from clinically diagnosed AD according to the criteria of Hanifin & Rajka (1), and if they reported suffering from AD during the last 3 months prior to the study. They were not allowed to use any itch-related medication at least 24 h prior to the examination and no high-potent itch-reducing medication on a regular basis. Additionally, they were excluded if they had already joined an education program for AD patients. Healthy controls as well as AD patients who suffered from any other somatic or psychiatric disease were excluded from the study. Furthermore, participants were excluded if they had already participated in another study at our institute, because they would then know the observation laboratory which could influence their behavior. All participants received an expense allowance of €15 after they completed the study appointment.

Variables

Predictor variables. The predictor variables agreeableness, public self-consciousness and depression were measured using the following 3 validated questionnaires, which we also used in the former study that we aimed to replicate:

1. Neo-Five Factor Inventory (NEO-FFI (17)): This questionnaire contains 60 items and measures 5 personality traits: agreeableness, extraversion, openness to experience, conscientiousness and neuroticism. In this study we were especially interested in the personality trait agreeableness. Persons scoring high on this trait can be described as empathic, cooperative, kind and polite instead of aggressive, stubborn or manipulative (18).
2. The Self-Consciousness-Scale (SCS; (19)) comprises 27 items and measures private as well as public self-consciousness. In this study we were especially interested in the scale public self-consciousness. Subjects scoring high on public self-consciousness pay much more attention to how they are seen by others.
3. The German version of the Hospital Anxiety and Depression (HADS-D; (20)) scale is a 14 item-questionnaire which measures clinically relevant signs of depression and anxiety. In this study we were especially interested in the scale depression.

Even though our main interest was to replicate the significant relationships between induced itch and scratching and the above-named personality characteristics, we applied the whole NEO, SCS and HADS in order to be able to also look at whether this time the other scales of the questionnaires were also not related to induced itch and scratching.

Criterion variables. Induced itch and induced scratching were considered as criterion variables. To determine induced itch, itch intensity was measured by self-ratings immediately after the presentation of the videos (also see procedure) using visual analogue scales ranging from 0–10. Itch increase from the control video (CV) to the experimental video (EV) was calculated by subtracting self-rated itch intensity immediately after the CV from itch intensity measured immediately after the presentation of the EV.

To determine induced scratching, the number of scratch movements during the whole presentation of the EV and CV was counted by two independent raters. Before counting, the raters were instructed by an experienced dermatologist (UG) on how to differentiate between scratching and simple touching. Scratching was defined as any movement including rubbing, while touching was characterized as movements of an extremity without rubbing (also see 15)). The interrater-reliability was highly significant with $r \geq 0.88$; $p \leq 0.001$ in all cases.

Additional variables. In addition, the Patient-Oriented-SCORAD (PO-SCORAD; 21) was measured in order to be able to determine the severity of AD. The PO-SCORAD is an instrument which assesses the extent of the skin symptoms as well as the intensity of 6 objective and two subjective symptoms (21).

Procedure

Patients and healthy controls came in groups of 3 or 4 to our observation laboratory. Patients and healthy controls were examined separately. The study was announced as a study on "the evaluation of teaching material concerning our skin and its function". This title was chosen to blind the subjects to the real intention of the study. Thus, they did not know that the videos were supposed to induce itch and scratching. As soon as they arrived at our laboratory, all participants were asked to sit down in a dimly-lit room. The participants were separated by divider walls in order not to influence each other. They were also asked not to talk to each other, drink or eat during the investigation. After giving their written informed consent, they were then presented with 3 videos in counterbalanced order (also see itch induction). In between the video presentations a 20-min wash-out period took place, during which the patients filled in validated questionnaires to assess the predictor and control variables. At the end of the investigation

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Table I. Timeline of the study visit

Time (min)	0	10	20 30	40	50 60	70	80 90
Study period		Video 1	Wash-out period 1	Video 2	Wash-out period 2	Video 3	
Action	Information on the study and informed consent	Measurement of scratching behavior	Evaluation of the first video; NEO-FFI	Measurement of scratching behavior	Evaluation of the second video; HADS, SAM, measurement of socio-demographic data	Measurement of scratching behavior	Evaluation of the third video Debriefing

Each participant was shown a control video (CV) and two experimental videos (EV; on skin diseases and crawling insects). However, in this study, we were only interested in the itch and scratching provoked by one EV in comparison to the CV. Thus, the third study period is marked grey. Patients who were presented with two EVs before the CV were not included in this study, because here a cumulative effect of itch/scratching might have occurred.

all participants were debriefed on the real intention of the study and had the possibility to ask questions about the study (for the procedure of the study, also see **Table I**). For this study, we were only interested in the reaction to one of the EVs.

Itch induction

Itch was induced by the presentation of an EV which either dealt with crawling insects (EV1) or skin diseases (EV2). Each video contained 9 pictures that were presented as a slide show. While seeing the pictures, a speaker (UG) talked in the background about either skin diseases (EV2) or crawling insects (EV1). The number of itch inducing words (e.g. itch, scratching, crawling) was equal in both videos. There was no difference in induced itch between the videos (also see results). The CV which was used as a baseline measure also included 9 pictures that were presented as a slide-show. The topic of the CV was "skin – the communication organ". The same speaker that talked in the EV also talked in the CV. Each video (CV; EV1 and EV2) lasted approximately 9.5 min. The order of video presentations was counterbalanced in order to avoid order effects of the videos: There were 11 subjects in each group who first watched the CV and then the EV, and there were 12 subjects in each group who were first presented with the EV and then the CV.

Statistical analyses

The two main hypotheses tested in this study were:

Hypothesis 1 (H1): Agreeableness and self-consciousness are significant predictors of induced scratching in patients with AD.

Hypothesis 2 (H2): Depression is a significant predictor of induced itch in patients with AD.

Statistical analyses were conducted using SPSS 22. The statistical method used to test H1 and H2 was a regression analysis, which either included the scales "agreeableness" and "public self-consciousness" (H1) or "depression" (H2) as predictor(s) of induced scratching (H1) or induced itch (H2) respectively. In case the regression analysis revealed that the criterion variable could be significantly predicted by a predictor variable, we tested whether the unstandardized and standardized residuals were normally distributed, which was the case. In order to verify that in this study – as in the previous study – the other personality characteristics were not related to induced itch and scratching, correlation analyses were conducted in a second step. To compare participants with and without AD with regard to socio-demographic data, personality, depression and anxiety, *t*-tests for independent samples were computed.

RESULTS

Sample characteristics

AD patients and healthy skin controls were similar in the distribution of gender: In the group of AD patients there were 20 females and 3 males, while in the group of healthy controls there were 21 females and 2 males. AD patients did not differ from healthy controls regarding age or education level ($p > 0.05$). The mean ± SD age in the group of AD patients was 24.3 ± 3.2, while it was 24.4 ± 3.4 in the group of healthy skin controls. In each group, 22 subjects had a university entrance diploma. Patients and healthy controls did not differ regarding depression [T (44) = 0.884; $p = 0.381$] nor public self-consciousness [T (44) = 1.481; $p = 0.146$], but AD patients scored significantly higher on the scale agreeableness than healthy skin controls [T (34.949) = –2.522; $p = 0.016$]. At the time of investigation, patients with AD had a mean PO-SCORAD of 36.3 ± 11.3 (range: 3.5–55.3). Nineteen patients suffered from a moderate PO-SCORAD, two from severe AD and two from mild AD.

Manipulation check "itch induction"

T-tests for dependent groups indicated that a significant increase in itch was induced by the EV [T (45) = –5.515; $p \leq 0.001$], scratching was by trend induced by the EV [T (45) = –1.740; $p = 0.089$]. The mean ± SD itch intensity during the CV was 1.43 ± 2.42, whereas it was 4.33 ± 3.74 during the EV. The mean ± SD number of scratch movements during the CV was 3.16 ± 2.59, whereas it was 3.82 ± 3.38 during the EV [see also **Fig. 1**]. Itch intensity and scratching behavior that occurred during the presentation of EV1 (video on crawling insects) and EV2 (video on skin diseases) did not differ [all $p \geq 0.110$]. Moreover, there were no significant differences in induced itch and

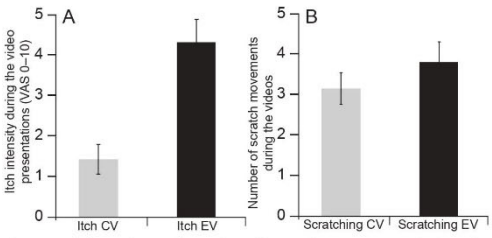

Fig. 1. Itch intensity and number of scratch movements during the presentation of the control video (CV) and experimental video (EV). The presentation of the EV to a significant increase in itch (A: $p < 0.05$) and by trend to an increase in scratching (B: $p < 0.1$).

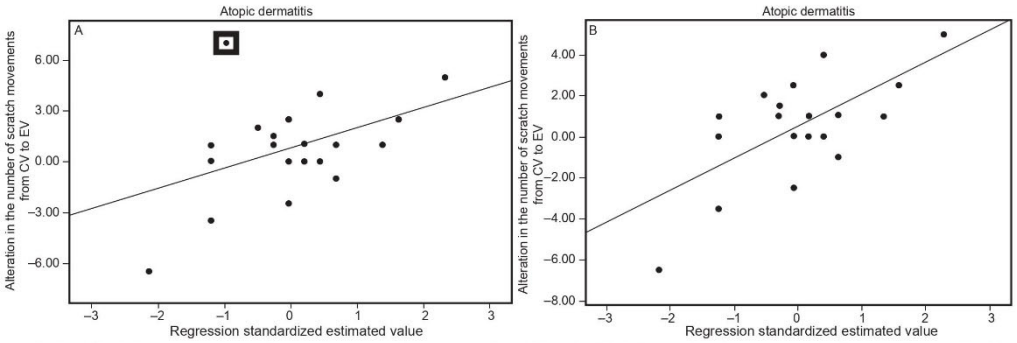

Fig. 2. Results of the regression analyses. The regression analyses showed that 15.5% of the variance in induced scratching could be predicted by agreeableness (A). After excluding one outlier (circled in A), 38% of the variance in the number of scratch movements could be explained by agreeableness (B).

scratching between patients with AD and healthy skin controls [all $p \geq 0.151$].

Results of the regression analyses

The regression analysis revealed that in patients with AD, induced scratching could be predicted by the personality variable "agreeableness" [F (1/22) = 5.022; $p = 0.036$], while public self-consciousness was not significantly associated with induced scratching in this study [r = –0.013; $p = 0.952$]. Agreeableness was able to explain 15.5% of the variance of induced scratching in patients with AD. Again, low agreeableness was related to more induced scratch movements [**Fig. 2**]. When taking a closer look at the results of the regression analysis [Fig. 2A], it becomes obvious that it is justifiable to regard the values of one patient as outliers. In this patient, the increase in scratch movements due to the video was greater than the mean increase in scratch movements plus two standard deviations. After excluding this patient, 38% of the variance of increase in scratch movements could be predicted by agreeableness [F (1/21) = 13.868; $p = 0.001$; corrected $R^2 = 0.38$; regression coefficient B = –4.397; standardized regression coefficient $\beta = -0.640$; Fig. 2B].

In addition, depression was not significantly related to itch induced by the EV in patients with AD in this study [r = 0.069; $p = 0.756$]. Also, none of the other assessed variables (extraversion, neuroticism, openness to experience, conscientiousness, self-consciousness, and anxiety) was significantly related to induced itch or induced scratching in patients with AD.

As in the previous study, also in this study none of all investigated psychological variables was significantly correlated with induced scratching in healthy skin controls [all $p > 0.05$]. However, private self-consciousness was positively correlated with induced itch and able to predict 14% of the variance of induced itch in healthy controls [F (1/21) = 4.585; $p = 0.044$; corrected $R^2 = 0.14$; regression coefficient B = 3.394].

DISCUSSION

The goal of this study was to replicate the findings of our former study (15), which showed that certain personality characteristics and depression were significantly related to induced itch and scratching, respectively, in AD patients. With the current study we were able to show again that the personality trait agreeableness was related to scratching induced by audiovisual stimulus material. However, in contrast to the findings of the former study, in this study, depression was not significantly related to itch increase due to audiovisual stimuli. Also, public self-consciousness did not turn out to be a significant predictor of induced scratching this time.

The finding that agreeableness and induced scratching are related in AD patients is of high interest for dermatologists and psychologists due to its robustness: This result is not only in line with our former study of AD patients, but also with the findings of our recent study in which we investigated the relationship in patients suffering from psoriasis (22), a skin disease which in many cases is also accompanied by intense pruritus (23). Thus, in patients with chronic itch, agreeableness seems to be an important psychological factor in determining at least partly whether patients with chronic itch tend to scratch or not when they are confronted with itch inducing stimuli. In this regard it is also of note that in the present study as well as in the study on patients with psoriasis (22), chronic itch patients displayed (in case of psoriasis at least by trend) higher scores regarding this personality characteristic than healthy controls. This could be seen as an adaptation process in patients with chronic itch which helps them not to react with impulsive scratching behavior in stressful social situations. When taking a closer look at the items of the scale agreeableness it becomes obvious that patients who score low on this scale can be regarded as stubborn, relentness, rather cool and not very cooperative. Due to the relationship repeatedly shown between low agreeableness and scratching it would in our

opinion be worth identifying patients with such psychological phenotypes during their visit to a dermatological practice. This would give dermatologists the chance to refer these patients to specialists working in the field of psychology/psychotherapy who could offer them certain psychological interventions that have already been shown to be or are regarded as beneficial in the treatment of itch and scratching (24, 25). Interventions we suggest to be especially helpful in patients scoring low on agreeableness are cognitive restructuring and anger management training. From our point of view it is reasonable to apply parts of Ellis' Rational Emotive Therapy (26) to identify irrational beliefs that provoke stubbornness and uncooperative behaviors in the special group of AD patients scoring low on agreeableness. This could then help them to reconsider the positive and negative effects of their beliefs in a next step. Subsequently these beliefs could then be replaced by rational, more functional beliefs (26). Moreover, anger management training, including role plays, which guide patients to react more calmly in anger provoking situations could also help rather aggressive and uncooperative patients by encouraging them to prevent impulsive behaviors directed towards their own skin in itch-inducing situations. On the other hand, one has to keep in mind that besides attitudes, other psychological factors like self-efficacy and intentions are also important factors influencing health-related behavior (in this case scratching) and that experimentally induced changes in attitudes, norms and self-efficacy only have small to moderate effects on health behaviors (27). From our point of view it is therefore an important task of future studies to investigate the size of effects of changing a combination of these variables on scratching behavior in itch inducing situations. Additionally, it would be worth investigating whether there are certain facets of agreeableness that show stronger relationships to induced scratching than others. It is, e.g., conceivable that particularly impulsive behavior directed towards oneself displays a more important predictor of induced scratching than impulsive behavior directed towards others. Unfortunately, in this study we did not apply a measuring instrument which allowed us to further investigate the relationship between induced scratching and different facets of agreeableness. This could be done in a future study.

There are further limitations to this study which should be addressed. With $n=46$ participants, the sample size of this study was rather small. However, due to the fact that this is already the third study (15, 22), which was able to show a significant negative relationship between induced scratching and agreeableness in patients with chronic itch, we are still convinced of the results. In order to be able to draw conclusions for both sexes though, future studies on the relationship between personality characteristics and itch/scratching should include men and women in an equal number, because it is known that men and women differ regarding the perception of experimentally induced itch (28). Moreover, the washout period of 20 min in between the videos was shorter than in the original study, where it lasted 30 min. This difference in study procedure was undertaken due to the fact that we also aimed to test two different EVs in this study, which led to a longer duration of the study visit.

Despite these limitations, this work increased our knowledge of the relationship between agreeableness and scratching behavior in patients with chronic itch. Moreover, in the future the findings might have clinical implications if experimentally changed attitudes in patients with chronic itch have been shown to have an effect on scratching in itch-inducing situations.

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7.7 Publikation 5

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Agreeableness and self-consciousness as predictors of induced scratching and itch in patients with psoriasis

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Abstract

Purpose: Psoriasis (PS) is a frequent skin disease accompanied by itch, a symptom that has been shown to be related to depression and self-consciousness. PS patients describe themselves as more agreeable than healthy controls (HC), a trait that might be protective against impulsive scratching. This study is the first to analyze the relationship between agreeableness and induced scratching and between depression, self-consciousness and induced itch in PS patients.

Methods: 24 PS patients and 24 HC were shown two videos: an itch inducing experimental video (EV) and a non-itch inducing control video (CV). Induced itch/scratching was determined by calculating the difference in itch intensity/number of scratch movements between EV and CV. Validated questionnaires were used to measure agreeableness, depression and self-consciousness.

Results: In accordance with our hypothesis, in PS patients public self-consciousness was significantly positively associated with induced itch ($r = 0.564$; $p < 0.001$), and agreeableness was significantly negatively associated with induced scratching ($r = -0.444$; $p < 0.05$). In HC, the relationship between public self-consciousness and induced itch and between agreeableness and induced scratching were positive, but not significant.

Conclusions: This study showed distinct findings for PS patients and HC regarding the relationship between agreeableness and induced scratching. The relationship between public self-consciousness and induced itch was positive in both groups. The distinct finding regarding agreeableness supports the idea that scoring low on this scale might be a protective factor for scratching in PS patients. Future research should investigate mediating factors of the outlined relationships.

Keywords: psoriasis, itch, scratching, self-consciousness, agreeableness

Introduction

Psoriasis (PS) is one of the most frequent chronic, inflammatory skin diseases [1, 2], which affects about 1–3% of the population [2-4]. It occurs in men and women with equal frequency [3], and is characterized by a symmetrical distribution of plaque, most often localized at the extensor areas of the elbows, the scalp and in lumbar regions [4]. Similar to other chronic skin diseases like atopic dermatitis, the majority of PS patients suffers from itch in times of exacerbations [5-8], which then depending on coping mechanisms leads to more or less intense scratching [9]. Here, it is important to emphasize that self-rated itch intensity and scratching as the behavioral response to itch stimuli should not be seen as interchangeable variables, but that a subjective itch sensation and scratching are two widely independent reactions to itch stimuli. There are studies, where only small to medium correlations between itch intensity and scratching were observed [10,11].

Although, of course, patients with PS do not all show the same personality structure, some personality characteristics seem to be more distinct in this patient group. PS patients describe themselves as more cooperative, more agreeable as well as less dominant than healthy controls [12], and report having more difficulties in expressing their anger than healthy men and women [13]. Whether this personality trait is related to coping with scratching impulses in this patient group is unclear so far. It is reasonable to assume though, that suppressing anger and instead being rather agreeable can be seen as one protective factor that withholds impulsive scratching behavior in patients with PS. This assumption has never been tested in this patient group before. In another group of patients with chronic itch, due to atopic dermatitis, the expected negative relationship between agreeableness and experimentally induced scratching could be shown [11]: Being not very agreeable and instead rather rude or excitable was related to a higher number of scratch movements in this study [11]. According to the findings outlined above, we assume that also in this study, agreeableness should be negatively related to impulsive scratching behavior, or in other words we hypothesize that high agreeableness could be seen as a protective factor for scratching in itch inducing situations.

Moreover, there are studies, relating patients' emotional constitution to self-rated itch intensity [14-17]. These studies suggest that being in a negative mood and/or depressed are related to an increased perception of unpleasant bodily sensations. In patients with PS in particular, a relationship between depression and self-rated itch intensity could be shown [15-

17]. Besides negative mood, also private self-consciousness referred to as the attention to inner feelings, attitudes and sensations [18] has been shown to be associated with the perception of aversive stimuli like itch [19]: Patients, who paid more attention to bodily sensations, also experienced greater itch intensity during itch inducing situations [19]. From a theoretical point of view, this finding is reasonable, because paying attention to oneself should go along with a higher susceptibility for changes in bodily sensations and the subsequent report of these symptoms. We believe that this association should be even more pronounced in patients with chronic (skin) diseases, because due to their disease they might recognize changes in their body earlier and evaluate them in a more differentiated way than healthy controls. Based on these empirical findings and theoretical considerations, we assume that private self-consciousness should be positively related to self-rated itch intensity in PS patients.

However, in our opinion, also another component of self-awareness, namely the tendency to pay attention to what other persons think about oneself ('public self-consciousness' [18]) should also be taken into consideration when investigating the relationship between itch intensity and personality characteristics in this patient group, because many PS patients feel highly stigmatized and excluded by others due to their skin appearance [20, 21]. We assume that particularly PS patients who, due to stigmatization experiences, are very aware of (negative) evaluations by others are also more susceptible to changes in their skin, including a change in itch intensity, because they fear the negative social consequences of their skin alteration.

Summarizing, with this study we aim to test the hypotheses that agreeableness is negatively associated with induced scratching and that depression and private as well as public self-consciousness are positively associated with induced itch in patients with PS. To the best of our knowledge, these hypotheses have never been analyzed in this patient group before. Information on the relationship between certain personality traits, depression and itch are of high value though, because they provide us with further hints about which subgroup of PS might profit from what kind of psychological intervention.

Method

Participants

43 patients with psoriasis and 198 healthy controls were recruited through written announcements at the campus of the University of Gießen, in supermarkets and by a circular mail which was sent to all students and employees of the Justus-Liebig-University. In addition, PS patients were recruited at the dermatology department of the university clinic. By means of a first telephone interview, exclusion and inclusion criteria were checked. Patients were included if they reported suffering from clinically diagnosed psoriasis during the last 12 months. Additionally, they were instructed not to use any itch-reducing topical medication at least 24 hours prior to the investigation. Exclusion criteria for patients with PS and healthy controls were the occurrence of any other somatic or psychiatric disease, the use of oral medication (except for hormonal contraceptives), being unreachable by telephone, missing time to take part in the study as well as participation in a prior study at our institute. 139 healthy controls and 4 PS patients had to be excluded based on these exclusion criteria. Thus, 39 patients with PS and 59 healthy controls took part in the study. Because we aimed to design the current study to be as similar as possible to a former study in which we investigated the relationship between induced itch/scratching and psychological variables in patients with atopic dermatitis [11], 14 of the patients examined were excluded after taking part in the study, because they had been shown *two* experimental videos instead of one before being presented the neutral video. The cumulative effect of the itch-inducing stimuli might have led to more itch/scratching and would thus have biased the results. In addition, one more PS patient had to be excluded post hoc, because he reported suffering from the autoimmune disease Hashimoto thyreoiditis. In total, 24 PS patients were included in the final sample. In addition, the same number of healthy controls was included in the final sample. These participants were chosen out of the pool of healthy controls in such a way that age, gender and the order of video presentation were stratified as good as possible in both groups.

Procedure

All participants came in groups of up to four persons to our observation laboratory, assuming that their reason of the study visit was to evaluate teaching material concerning the skin and its function. This cover story was invented in order not to influence the participants` scratching behavior and itch ratings. At the beginning of the investigation, participants were asked to sit

down in a shaded, low-stimulus room. They were separated by divider walls and asked not to speak to each other, eat or drink during the investigation. After giving their informed consent, they were shown the videos in counterbalanced order: The control video (CV) dealt with the topic 'skin - the communication organ', while the experimental video either dealt with skin diseases (EV1) or crawling insects (EV2; also see itch induction). During the video presentations, participants were video-recorded to make it possible to count their scratch movements afterwards (also see ethics). Whether the participants were shown the first or second EV was determined by randomization: A person not involved in data collection drew an envelope stating the order of the video presentations.

After the first and second video presentation a 'wash-out' period of 20 minutes followed, during which self-rated itch intensity and psychological variables were measured using questionnaires (see predictor variables). At the end of the investigation, the participants were informed about the true intention of the study (also see ethics) and got a €15 expense allowance for their attendance. The time-line of the study can be seen in Fig 1.

[Please put Fig. 1 here].

Itch induction

Itch was induced by a non-invasive method [11, 22], which might work through classical conditioning processes [23] and uses (audio-) visual material instead of pruritogens like histamine or cowhage that were used in other studies [e.g. 14, 24].

In this study, a video on crawling insects (EV1) as well as a video on skin diseases (EV2) was used to induce itch. EV1 contained pictures of flea- or mosquito bites on a human arm, bugs and crawling ants. EV2 included pictures of patients suffering from atopic dermatitis, urticaria and psoriasis. Additionally, pictures of scratch brushes and triggering factors were presented. The CV contained pictures showing, e.g., two touching hands, a woman taking a shower, the immaculate skin of two Barbie dolls and naked feet of a family lying in bed. The pictures were presented as a slideshow. In every video the same speaker (UG) talked in the background about the particular topic. Each video lasted approximately 9.5 minutes and contained 9 pictures. The number of itch inducing words, which were chosen in agreement with two itch experts (JK and UG), was parallelized in both experimental videos.

Variables

Predictor variables

To measure agreeableness, depression and self-consciousness the following questionnaires were used:

- The *Neo Five-Factor Inventory* (NEO-FFI; [25]) was used to measure agreeableness.
- The *Hospital Anxiety and Depression Scale* (HADS; [26]) was used to measure depression.
- The *Self-Assessment Scale* (SAM; [18]) includes 27 items and was used to measure private and public self-consciousness. An item that is used to measure public self-consciousness e.g. is *'It is important for me, how others think about me'*, while *'I carefully observe my inner feelings'* is one item that is included in the private self-consciousness scale.

Criterion variables

Induced scratching was determined by subtracting the number of scratch movements which occurred during the presentation of the CV from the number of scratch movements which occurred during the presentation of the EV. In order to be able to differentiate between scratching and mere touching, two independent persons who rated the videos were instructed and calibrated by a skilled itch researcher (UG). Scratching was defined as any movement which included rubbing. The correlation between the two ratings concerning the number of scratch movement was $r > 0.99$ ($p < 0.001$).

Itch intensity was measured in the context of assessing the quality and effects of the video by a visual analogue scale (VAS) ranging from 0-10. The self-rated itch intensity was measured immediately after each video presentation. The criterion variable 'induced itch' was calculated by subtracting self-rated itch intensity measured immediately after the EV from self-rated itch intensity measured immediately after the CV.

Control variables

Age, gender and years of education were assessed as control variables. Additionally, in order to be able to include the severity of psoriasis as a predictor of itch/scratching, patients filled in the self-assessed psoriasis area and severity index (SA-PASI), which is a validated self-measurement of psoriasis severity [27-29]. This measurement assesses the extent of affected skin, the intensity of the symptoms, color, scaliness and induration as well as the overall

severity by means of visual analog scales. The SAPASI ranges between 0 – 72, with higher scores indicating more severe disease [27-29].

Ethics

The study design was in accordance with the ethical standard of the local ethics committee (167/10) and the Declaration of Helsinki. In order to blind the subjects about the measurement of itch and scratching, a cover story was told at the beginning of the investigation that led the participants to believe that they were taking part in a study on measuring the quality of teaching material. The study was announced as a study on 'evaluation of video-material concerning different functions of our skin – a comparison of patients with psoriasis and healthy controls.' Informed consent was obtained from patients and healthy controls in the study after the nature of the procedure had been fully explained to them. The participants` right to privacy was not infringed. They were free to withdraw from the study at any time. At the end of the observation, a debriefing was conducted, during which all participants were informed about the true intention of the study. Afterwards they had the opportunity to ask questions.

Statistical analyses

The statistical analyses were conducted using SPSS 21. Kolmogorof-Smirnov Goodness of Fit Tests indicated that the assumption of normal distribution was not violated for any predictor or criterion variable. Group differences between PS patients and healthy controls were tested by t-tests for independent samples or χ^2-tests. To test whether itch and scratching could be induced by the presentation of the EV ('manipulation check'), 1-way analyses of variance with repeated measures and the factor 'video' were conducted in PS patients and healthy controls separately. In addition, a 2-way analysis of variance using the factor 'group' as an additional factor was computed in order to test whether PS patients and healthy controls differed concerning induced itch/scratching. Furthermore, t-tests for independent samples were conducted to analyze whether the two EVs led to significant differences concerning the experience of itch.

In order to answer the research questions of this study, correlation analyses were calculated first in order to identify predictor variables significantly correlating with the criterion variables 'induced itch' and 'induced scratching'. Afterwards, two stepwise linear regression analyses

were conducted for both groups (skin patients and healthy controls) including either induced itch or induced scratching as criterion variables. Variables that were identified as significantly correlating with the criterion variable were entered in the first step of the regression analysis. Afterwards, moderated regression analyses were calculated using the SPSS macro Process, whose use is described by Hayes [30]. Health status (psoriasis vs. healthy) was entered as potential moderator in the regression analyses either predicting induced itch or induced scratching.

Results

Sample characteristics

The final sample consisted of 24 PS patients and 24 healthy controls. 12 of the PS patients were male and 12 female, while 11 of the healthy controls were male and 13 were female. The mean age of the PS patients was 31.8 years (SD = 11.7). The mean age of the healthy controls was 32.1 years (SD = 12.1). The groups did not differ in age [t (46) = .109; p = .914]. 15 of the PS patients and 14 of the healthy controls lived in a partnership. 19 of the PS patients and 20 of the healthy controls attended school for more than 12 years. The mean SAPASI was 4.8 (± 2.8).

T-tests indicated no significant group-differences concerning depression [t (46) = -1.328; p = 0.191], public self-consciousness [t (46) = -0.922; p = 0.362] or private self-consciousness [t (46) = -0.443; p = 0.660]. By trend, PS patients and healthy controls differed concerning agreeableness [t (46) = -1.860; p = 0.069] in that way that the PS patients were more agreeable (Table 1).

[Please put Table 1 here]

Manipulation check 'itch induction'

The results of the 1-way analyses of variance with repeated measures indicated that itch and scratching were induced by the presentation of the EV. In patients with PS the itch intensity immediately after the EV (3.89 ± 3.17) was significantly higher than immediately after the CV (1.18 ± 1.44; [F (1/23) = 17.349; $p \leq 0.001$; $\eta^2 = 0.430$]). Also, healthy controls reported a significant higher itch intensity immediately after the EV (4.23 ± 3.62) than after the CV (0.94 ± 1.48; [F (1/23) = 25.333; $p \leq 0.001$; $\eta^2 = 0.524$]). Patients and healthy controls did not differ concerning induced itch (video*group effect: [F (1/46) = 0.393; p = 0.534; $\eta^2 = 0.008$]).

Furthermore, PS patients scratched significantly more often when watching the EV (5.02 ± 4.49) than when watching the CV (3.52 ± 2.96; [F (1/23) = 5.154; p = 0.033; $\eta^2 = 0.183$]). Also, healthy controls scratched more often during the presentation of the EV (5 ± 5.42) than during the presentation of the CV (2.96 ± 2.68); [F (1/23) = 6.995; p = 0.014; $\eta^2 = 0.233$]). Here, again, PS patients and healthy controls did not differ concerning induced scratching (video*group-effect: [F (1/46) = 0.284; p = 0.597; $\eta^2 = 0.006$]).

Furthermore, t-tests for independent measures revealed that the itch induced by EV1 did not significantly differ from the itch intensity induced by EV2 [t (46) = -0.265; p = 0.792]. Also the number of scratch movements that occurred during the presentation of EV1 did not significantly differ from the number of scratch movements that occurred during the presentation of EV2 [t (46) = -1.204; p = 0.235]. Similar results were observed, when t-tests for independent groups were calculated separately for patients and controls [all $p \geq 0.222$].

Figure 2 illustrates the mean itch intensity (±SEM), which was measured immediately after the video presentations and the mean number of scratch movements (±SEM), which was observed during the video presentations separately for patients with PS and healthy controls.

[Please put Fig. 2 here]

Results of the correlation and regression analyses

The correlation analyses indicated that in the group of healthy controls none of the possible predictor variables significantly correlated with induced itch or scratching [all $p > 0.05$]. In contrast, in the group of PS patients, induced itch significantly correlated with public self-consciousness [r = 0.564; p = 0.004]. Furthermore, a significant negative correlation was observed between induced scratching and agreeableness in the patient group [r = -0.444; p = 0.03]. Interestingly, the SA-PASI neither correlated with induced itch nor with induced scratching [$p > 0.05$]. Please, see Table 2 and Fig. 3 for correlations and scatterplots.

[Please put Table 2 and Fig. 3 here]

The regression analyses confirmed these associations. They indicated that induced itch could be significantly predicted by public self-consciousness [F (1/23) = 10.261; p = 0.004; corrected R^2 = 0.287] in PS-patients, while agreeableness was a significant predictor of induced scratching in the patient group [F (1/23) = 5.401; p = 0.030; corrected R^2 = 0.161; also see Table 3].

[Please put Table 3 here]

The subsequent moderated regression analyses revealed a significant interaction effect when predicting induced scratching by agreeableness [F (1/44) = 7.0305; p = 0.0111; change in R^2 =

0.1366], but no significant interaction effect when induced itch was predicted by public self-consciousness [F (1/44) = 0.6182; p = 0.4359; change in R^2 = 0.0107].

Discussion

This study is the first to investigate the role of certain personality characteristics for induced itch and scratching in PS patients. The results indicate that our hypothesis concerning induced scratching in PS patients could be verified: PS patients scoring low on agreeableness showed a higher increment in scratch movements than patients scoring high on this personality scale. This result is in line with the results of a former study [11], in which low agreeableness was also associated with a higher increase in scratching in patients suffering from chronic itch due to atopic dermatitis. In this context it is interesting, that in the current study the PS patients were by trend more agreeable than healthy controls, a result which is in accordance with the finding of another study, where PS patients were shown to express less verbal aggression than healthy controls in anger inducing situations [31]. Being more agreeable could be seen as a functional coping mechanism that prevents patients from impulsive behaviors. It is reasonable to assume that being not very agreeable, but instead excitable and competitive leads to a higher arousal in itch-inducing situations, which then might result in impulsive self-directed activities. Supporting this idea, also in macaques, it was shown that self-directed behavior, defined as the sum of scratching, self-grooming and body shaking, increased after aggressive social interactions [32]. In future studies the idea that being not very agreeable, but rather angry and tensed increases induced scratching could be further illuminated by inducing anger in an experimental setting before inducing itch. A strategy to induce anger could be by giving negative feedback to patients about their personality like it was done in a former study in PS patients [31]. Moreover, in this context it would also be interesting to differentiate between patients suffering from the early (at the age < 20 years) and late onset psoriasis, because patients with early onset were shown to score higher on 'embitterment', 'mistrust' and 'verbal trait aggression' [33] - a finding which allows the assumption that patients suffering from this type of psoriasis would also show more scratch responses in itch inducing situations compared to patients with the late onset psoriasis. Interestingly, the negative relationship between agreeableness and induced scratching only occurred in PS patients, but not in healthy controls.

Besides this first finding, as a second result, we were able to show a positive relationship between public self-consciousness and induced itch in PS patients: Almost 30% of the variance of induced itch could be predicted by the tendency to pay attention to what other people think about one self. One possibility to interpret this finding is that especially patients, who

experienced many negative social reactions because of their skin appearance, became more and more insecure and aware of their disease. This insecurity could be seen as a vulnerability factor of itch which is brought to bear in itch inducing situations. It could therefore be of clinical importance to identify highly insecure PS patients and offer them psychological interventions to improve their disease related insecurities. One intervention that could be worth to apply to such a patient group is the acceptance and commitment therapy (ACT; [34]), which aims to alter patients' attitudes towards and the coping with their (chronic) disease. Concerning this result, it is interesting though, that the interaction effect did not become significant and that by trend also a relationship between public self-consciousness and induced itch could be seen in healthy controls. Therefore, we assume that insecurity induced by negative judgements by others does not only alter induced itch in skin patients, but also in the general population – a finding which should be investigated in the future.

Interestingly, contrary to our hypothesis, private self-consciousness and depression were not related to induced itch in this study. One possibility to explain these missing links could be that negative emotions and self-awareness are only associated with itch, when they lead to certain illness-related cognitions and behaviors. Thus, when interpreting the relationships between personality characteristics and itch, it is also important to take into consideration other mediating factors that are included in the biopsychosocial model of chronic itch [35]. It is reasonable to assume that depression and itch are only associated e.g. when depression leads to a certain way of illness-related thinking or the negotiation of social support. For future studies it would therefore be desirable to not only assess personality characteristics, but also possible mediating psychological variables like social support or coping. In a recently published study we e.g. found a highly significant relationship between illness-related cognitions as a kind of cognitive coping and itch in patients with atopic dermatitis [36]. These possible mediating factors should also be analyzed in patients with PS.

Surprisingly, in this study the chronic itch patients did not react with a higher increase in itch and scratching than healthy controls. This finding is in contrast to two former studies, in which patients with atopic dermatitis reacted to (audio-)visual itch cues with a higher itch intensity and more scratch responses than healthy controls [11,37]. At this point we can only speculate about these contrary findings and hypothesize that PS patients in the current study had more functional coping strategies than the patients with atopic dermatitis that were investigated in

the previous studies. Also, it is possible that in PS patients the biochemical processes that lead to itch due to (audio-)visual itch cues (which we do not know yet), take longer than in patients with atopic dermatitis. It would certainly be interesting to measure itch mediators like interleukin 31 (IL-31; 38,39) in the skin before and after (audio-)visual itch induction to get a better idea of what happens in the skin of chronic itch patients when being exposed to itch cues.

Of course there are also some limitations to this study, which should be discussed. First of all, the sample size of this study was rather small and even though a-priori hypotheses had been formulated, our findings should be seen as results with explorative character and should only be taken as a first hint rather than as the basis of clinical implications. In order to derive clinical implications from this study, further investigations in larger samples also including patients with more severe PS would be needed. Also, one should keep in mind that the findings of our study are not causal but correlative, which means that no 'if-then-conclusions' can be drawn from it. Instead our study 'only' showed that PS-patients scoring high or low on a certain questionnaire scale were more prone to experience itch or scratch. Randomized, controlled trials, in which e.g. anger would be induced experimentally, could provide a deeper insight in whether agreeableness is a factor influencing scratching behavior in chronic itch patients.

Despite these limitations, this study underlines the importance of personality characteristics for induced itch and scratching in patients with psoriasis. It thus expands the results of a former study which found a link between personality and induced itch/scratching in patients with atopic dermatitis [11].

All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2000. Informed consent was obtained from all patients for being included in the study.

All authors declare that they have no conflict of interest.

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Fig. 1. Timeline of the study

In this study only the scratch responses during the presentations of video 1 and 2 as well as the itch intensity immediately after the presentation of videos 1 and 2 were analyzed. Therefore, the third video presentation is marked dark grey in the figure. Patients who had seen two itch inducing videos before the presentation of the neutral video were excluded due to a possible cumulative effect of itch/scratching. The order of video presentation was counterbalanced in both groups (healthy controls and patients with psoriasis).

Fig. 2. Manipulation check

a) Self-rated itch intensity (mean ± SEM) immediately after the presentation of the videos and b) the number of scratch movements (mean ± SEM) during the presentation of the videos. The dotted line represents the patients with psoriasis (n = 24). The continuous line represents the healthy controls (n = 24).

Fig. 3. Scatterplots

Public self-consciousness is significantly associated with induced itch (A; corrected $R^2 = 0.287$) and agreeableness is significantly associated with induced scratching (B; corrected $R^2 = 0.161$) in patients with psoriasis.

Table 1. Sample characteristics.

Variables	Patients with psoriasis (n = 24) Mean ± SD (range)	Healthy controls (n = 24) Mean ± SD (range)
Agreeableness	2.63 ± 0.48 (1.25 – 3.25)	2.38 ± 0.44 (1.5 – 3)
Depression	3.77 ± 2.59 (0 – 11)	2.83 ± 2.28 (0 – 7)
Public self-consciousness	3.42 ± 0.60 (2.36 – 4.29)	3.25 ± 0.64 (1.71 – 4.43)
Private self-consciousness	3.60 ± 0.48 (2.54 – 4.46)	3.53 ± 0.61 (2.38 – 4.54)

Description of patients with psoriasis and healthy controls concerning the assessed personality characteristics.

Table 2. Results of the correlation analyses

	Agreeableness	Private self-consciousness	Public self-consciousness	Depression
Induced scratching in *PS patients* (n = 24)	-.444*	.046	.174	-.165
Induced itch *in PS patients* (n = 24)	-.289	.283	.564**	-.267
Induced scratching *in healthy controls* (n = 24)	.314	.048	.317	-.024
Induced itch in *healthy controls* (n = 24)	.117	.227	.382^{+}	.401^{+}

The results of the Pearson correlation analyses revealed a significant correlation between induced scratching and agreeableness ($p < 0.05$) as well as between induced itch and public self-consciousness ($p < 0.01$) in patients with psoriasis. In healthy controls no significant associations between induced itch/scratching and the assessed personality characteristics occurred. Correlations that are labelled with a '+' were significant by trend ($p < 0.1$).

Table 3. Results of the regression analyses in patients with psoriasis (n = 24).

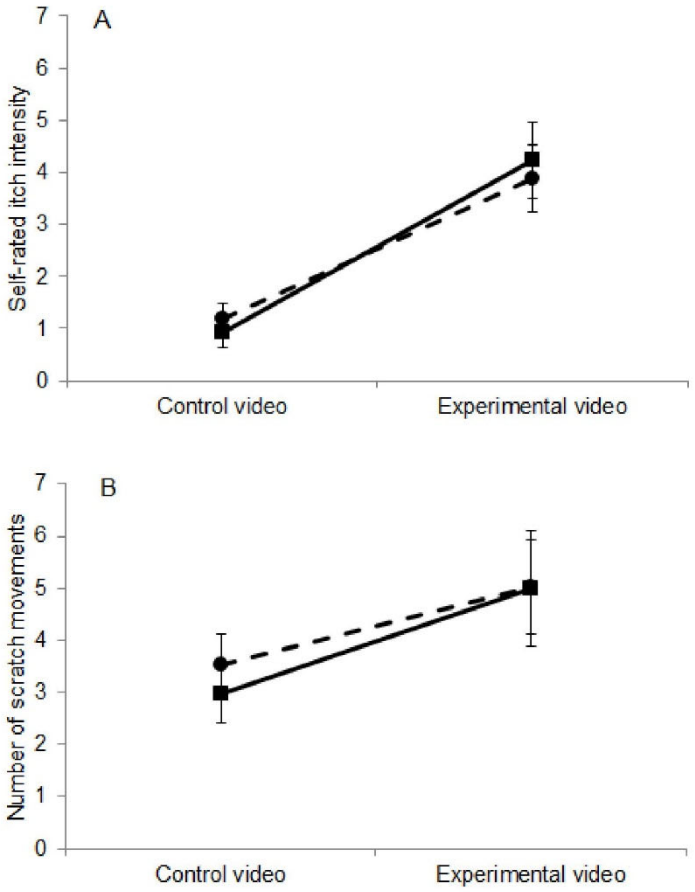
	Predictor variable	Regression coefficient B	Standard error	Beta	T	Significance
Criterion variable: induced itch	Constant	-7.538	3.247		-2.322	0.030
	Public self-consciousness	3.000	0.937	0.564	3.203	0.004
Criterion variable: induced scratching	Constant	9.375	3.442		2.723	0.012
	Agreeableness	-3.000	1.291	-0.444	-2.324	0.030

The first regression analysis revealed that public self-consciousness was a significant predictor of induced itch in patients with psoriasis (n = 24; corrected $R^2 = 0.287$). The second regression analysis indicated that agreeableness significantly predicted induced scratching in patients with psoriasis (n = 24; corrected $R^2 = 0.161$).

Figure 1.

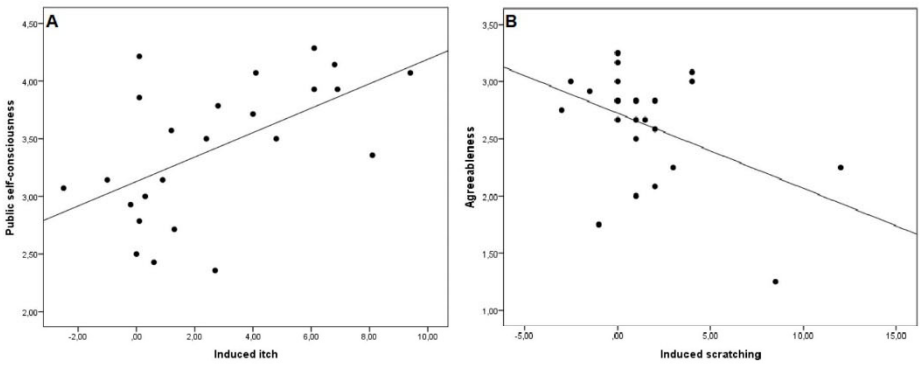
Time (min)	0	10	20	30	40	50	60	70	80	90
Study period		Video 1	Wash-out period 1		Video 2	Wash-out period 2		Video 3		
Action	Information on the study and informed consent	Measurement of scratching behavior	Evaluation of the first video; NEO-FFI		Measurement of scratching behavior	Evaluation of the second video; HADS, SAM, measurement of socio-demographic data		Measurement of scratching behavior	Evaluation of the third video	Debriefing

Figure 2.


A
Self-rated itch intensity
7
6
5
4
3
2
1
0
Control video
Experimental video
B
Number of scratch movements
7
6
5
4
3
2
1
0
Control video
Experimental video

28

Figure 3.


A
Public self-consciousness
4,50
4,00
3,50
3,00
2,50
2,00
-2,00
,00
2,00
4,00
6,00
8,00
10,00
Induced itch
B
Agreeableness
3,50
3,00
2,50
2,00
1,50
1,00
-5,00
,00
5,00
10,00
15,00
Induced scratching

7.8 Publikation 6

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MINI REVIEW

Role of personality and expectations for itch and scratching induced by audiovisual itch stimuli

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Abstract

Itch is an unpleasant, bodily sensation, which – similar to pain – evokes behavioral reactions. As a response to itch, people start scratching. There are different ways to provoke itch and subsequent scratching in experimental settings. A non-invasive method to induce itch and scratching is the presentation of itch-related (audio-) visual stimulus material, like slide-supported lectures on skin diseases or crawling insects. Also, watching videos showing other people scratching provokes itch and the desire to scratch. In this review, we focus on psychological factors, which were shown to be associated with itch and scratching provoked by (audio-) visual itch stimuli. First, we summarize the findings on the relationship between personality characteristics and (audio-) visually induced itch. Agreeableness and self-consciousness were shown to be associated with induced itch and scratching in patients with chronic skin diseases, while neuroticism was linked to induced itch in healthy subjects. Second, we present results of a recent study, in which we altered the expectations towards audio-visually induced itch and scratching by changing the information given on upcoming itch stimuli. It was shown that subjects being informed about itch stimuli in a neutral way displayed a shorter scratch duration in itch inducing situations than subjects having catastrophizing expectations. Also, the increase in scratch duration and in the number of scratch movements induced by audiovisual itch stimuli was higher when the patients were not informed about itch induction. Thus, in itch patients neither catastrophizing nor trivializing symptoms seems to be helpful.

The itch sensation and its provocation by audiovisual stimuli

Even though itch and pain are different sensations, they share several similarities (Ständer and Schmelz, 2006). Like pain, itch is an unpleasant sensation, which decreases the quality of life of patients with chronic itch to a large extent (Zachariae et al., 2012). As a behavioural reaction to itch, people start scratching the itchy part of their skin. At first, scratching reduces itch, but later on even increases the sensation. Often, a vicious cycle develops (Leknes et al., 2007).

To be able to investigate physiological processes during itch, one has to be able to provoke itch in experimental settings. Often, pruritogens like cowhage or histamine are applied to the skin of the subjects (e.g. Papoiu et al., 2011a). Another method, which has become more and more popular during the last 5 years, is the induction of itch and scratching by the presentation of certain (audio-) visual stimuli (Niemeier et al., 2000; Papoiu et al., 2011b; Holle et al., 2012; Lloyd et al., 2013; Mochizuki

What does this Review add?

- This review summarizes what is known about the association between personality characteristics and (audio-) visually induced itch and scratching in patients with chronic itch and healthy controls.
- Moreover, we present data on how expectations regarding upcoming itch stimuli alter induced itch intensity and scratching behaviour in patients with chronic itch and healthy controls.

et al., 2013; Ward et al., 2013; Schut et al., 2014, 2015a,b). Using this method, researchers took advantage of the effect that patients and skin-healthy controls reacted with itch sensations and scratching when they were shown videos or pictures of itch-related stimuli like skin diseases, crawling insects or scratching behaviour. In comparison to other itch induction methods, the (audio-) visual stimulation of itch has the advantage that no skin manipulation is needed, which itself can evoke anxiety or unpleasantness and thus could even increase the itch sensation. Moreover, in our opinion, (audio-) visual itch stimulation is very similar to what happens in real life: Subjects are confronted with itch stimuli and due to classical conditioning processes, the stimuli associated with itch trigger the symptom.

There are many studies which have shown that the variance in the response to itch stimuli greatly differs between subjects. It is important to recognize that the extent to which subjects react to itch stimuli does not only depend on the itch stimulus (e.g. cowhage or histamine, Papoiu et al., 2011a) but also on the psychological status of the subjects. In a study in which histamine was used to induce itch, mood was an important factor influencing the intensity of the reaction to itch stimuli (Van Laarhoven et al., 2012): Women in a positive emotional state reported less intense itch than women who had negative emotions. Besides, mood, also other psychological factors like stress, itch-related cognitions, personality and expectations towards itch stimuli have been shown to be associated with itch sensations in healthy subjects and patients with itchy skin diseases (e.g. Kodama et al., 1999; Verhoeven et al., 2008; Van Laarhoven et al., 2011; Schut and Kupfer, 2013; Schut et al., 2014, 2015b,c). This review focuses on personality and expectations as psychological factors related to itch induced by (audio-) visual stimuli (Holle et al., 2012; Schut et al., 2014, 2015b).

Role of personality characteristics for audiovisually provoked itch and scratching

The individual way people feel, behave and think represent their personality (Amelang and Bartussek, 2001; Caspi et al., 2005). By now there is a wide consensus that there are five broad personality factors, namely extraversion, neuroticism, openness to experience, agreeableness and conscientiousness (Amelang and Bartussek, 2001; Caspi et al., 2005).

In studies, in which the association between audiovisually induced itch and personality characteristics was assessed (Schut et al., 2014, 2015b), self-consciousness as the tendency to pay attention to inner feelings and sensations ('private self-consciousness') and to what others think about oneself ('public self-consciousness'; Filipp and Freudenberg, 1989) were also examined. This was done due to the fact that in former studies, itch intensity was related to focusing on oneself (Van Laarhoven et al., 2010). Moreover, especially in patients with chronic skin diseases, their own appearance seems to be of high relevance due to experienced stigmatization (e.g. Hrehorów et al., 2012). We hypothesize that these experiences might lead to more arousal and psychological burden, which again might increase the impulse of scratching and itch.

Interestingly, the results of the studies on the associations between audiovisually induced itch and personality characteristics differed between patients with chronic itch and healthy controls (Schut et al., 2014, 2015b): One study, which investigated the relationship between induced itch, scratching and personality in patients with atopic dermatitis showed that induced scratching could be predicted to a large extent, namely 53.4%, by agreeableness and public self-consciousness. AD patients, who displayed a personality that was characterized by not being very empathetic, cooperative or tender-hearted, but instead rather cruel, competitive and unfriendly (low agreeableness) and at the same time were very much concerned about what other people thought about them (high public self-consciousness) showed more induced scratch responses than patients with opposite personality characteristics (Schut et al., 2014). Interestingly, we found a similar relationship in psoriasis patients (Schut et al., 2015b). Here, again, agreeableness was negatively related to induced scratching ($r = -0.444$; $p < 0.05$), while in both studies no significant relationships between this personality factor and induced scratching were observed in *healthy controls*. Regarding induced itch, we also only found personality charac-

teristics to be significant predictors in patients with chronic itch, not in healthy controls. In patients with psoriasis, induced itch was significantly positively associated with public self-consciousness ($r = 0.564$; $p > 0.001$; Schut et al., 2015b). In another study investigating the relationship between visually induced itch and the big five personality factors in healthy subjects, neuroticism was positively related to itch increase ($r = 0.34$; $p > 0.05$; Holle et al., 2012). One has to point out though, that this correlation was smaller than the correlations found in the other studies and that a slightly different way of itch induction was used: Persons were shown videos of other persons scratching their arm.

Summarizing, it is obvious that further research is needed on the relationship between personality characteristics and (audio-) visually induced itch, but that up to this point at least, agreeableness has repeatedly been shown to be associated with induced scratching in patients with chronic itch. This is consistent with findings suggesting that disagreeableness may be linked to disease processes (Caspi et al., 2005).

Role of expectations for induced itch and scratching

Besides personality, expectations towards stimuli also alter the perception of and reaction to these. There are several studies, which showed that placebo and nocebo effects are of high relevance when investigating the perception of pain (e.g. Dobrila-Dintinjana and Načinović-Duletić, 2011; Colloca and Grillon, 2014). The placebo effect describes the effect that physical complaints can be affected in a positive way by positive expectations, while the nocebo effect includes the opposite: Negative expectations can lead to an increase in unpleasant physical complaints (Van Laarhoven et al., 2011). In a recently published meta-analysis, Van Laarhoven et al. (2015) were able to show the relevance of the placebo effect in itch treatments.

In a former study, it was shown that the intensity of itch stimuli in healthy subjects was significantly altered by verbal suggestions given before the application of the itch stimuli (Van Laarhoven et al., 2011): In the case where a negative expectation was evoked by explaining that 95% of the subjects experience itch and that 5% experience pain due to the stimuli, the evoked itch intensity was significantly higher than in the control condition, in which subjects expected the itch stimuli to evoke itch and pain with a low probability of 5%. In a recent study by Bartels et al. (2014), these findings were expanded in that it was shown that verbal suggestions in combination with classical conditioning processes had the greatest nocebo effects on induced itch intensity. In another, former study the effects of catastrophizing expectations compared with relativizing expectations on histamine-induced itch were investigated in patients with atopic dermatitis (Scholz and Hermanns, 1994).

All of these studies had in common that itch was induced by a skin-manipulating method and

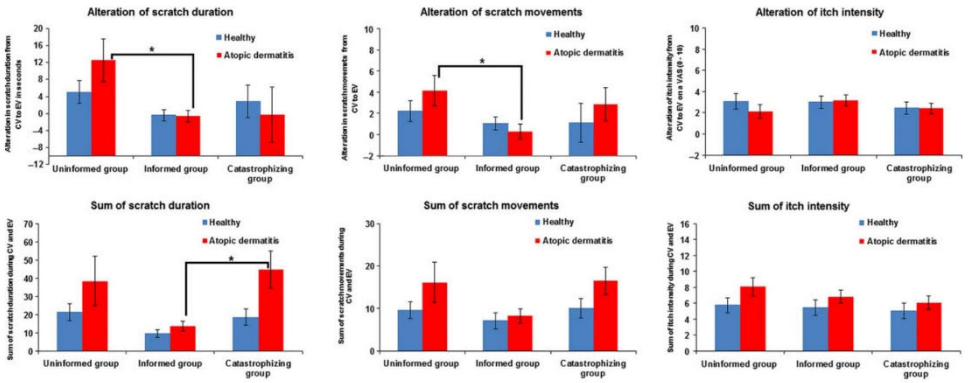

Fig. 1 Effects of different expectations about upcoming audiovisual itch stimuli on induced itch and scratching in patients with atopic dermatitis and healthy controls. The alterations of scratching (scratch movements and scratch duration) and itch intensity from CV to EV (upper row) are illustrated, as well as the sum of scratch movements, scratch duration and itch intensity during both video presentations (bottom row) as mean ± SEM.

not by audiovisual stimuli. Moreover, so far none of the studies has examined the effects of expectations on scratching as the response to itch. This brought up the question of whether expectations also alter audiovisually induced itch and scratching. To answer this question, we recently conducted a study in which we analysed the effects of expectations on audiovisually induced itch and scratching. In this study, 60 patients with atopic dermatitis and 60 healthy controls, stratified for age and gender, were randomized to one of three groups: the uninformed group (UIG) which did not receive any information about the upcoming itch stimuli, the informed group (IG) which was told that 'they would be shown videos which induce itch', and the catastrophizing group (CAG) which was told that 'they would be shown videos which very probably induce a very intense itch that is perceived as extremely unpleasant by many persons'. They were then shown two videos in counterbalanced order: an itch inducing experimental video (EV; a slide supported lecture on crawling insects) and a non-itch-inducing control video (CV). Itch intensity was measured after each video presentation by visual analogue scales (VAS 0–10). The number of scratch movements and the scratch duration during the video presentations was counted by two independent observers.

Interestingly, we only found differences between the groups (IG; UIG; CAG) in patients with atopic dermatitis, but not in healthy controls: During the video presentations, the CAG displayed a significantly longer scratch duration than the IG ($p < 0.05$). Moreover, the increase in scratch duration and in the number of scratch movements from CV to EV was significantly higher in the UIG than in the IG ($p < 0.05$; also see Fig 1). These findings were substantiated by the descriptive data of the non-significant differences (also see Fig. 1). The result that catastrophizing information on the upcoming itch stimuli led to a longer scratch response is consistent with the results of former studies, where negative expectations about the stimuli evoked more itch than neutral information (Scholz and Hermanns, 1994; Van Laarhoven et al., 2011). On the other hand, not being informed about the upcoming itch stimuli might have led to more arousal in the UIG than in the IG during the EV, which could have provoked more dysfunctional coping behaviour (scratching). This hypothesis should be tested by, e.g. asking patients of the UIG whether they felt more stressed during the EV than the IG.

Conclusion

Even though there are first results on how psychological factors contribute to (audio-) visually induced itch intensity and scratching, several questions have not yet been answered. It would, e.g. be of interest to investigate how other psychological factors like stress, mood, illness cognitions and mindfulness are related to this rather mind-related way of experiencing itch. Further research will help us to better understand this interesting phenomenon and the role of psychological factors.

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7.9 Publikation 7

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Contagious itch: what we know and what we would like to know

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All humans experience itch in the course of their life. Even a discussion on the topic of itch or seeing people scratch can evoke the desire to scratch. These events are coined "contagious itch" and are very common. We and others have shown that videos showing people scratching and pictures of affected skin or insects can induce itch in healthy persons and chronic itch patients. In our studies, patients with atopic dermatitis (AD) were more susceptible to visual itch cues than healthy. Also, personality traits like agreeableness and public self-consciousness were associated with induced scratching in skin patients, while neuroticism correlated with induced itch in healthy subjects. The underlying course of contagious itch is not yet fully understood. It is hypothesized that there are human mirror neurons that are active when we imitate actions and/or negative affect. Until now, there has been only limited data on the mechanisms of brain activation in contagious itch though. We have barely begun to understand the underlying physiological reactions and the triggering factors of this phenomenon. We summarize what we currently know about contagious itch and provide some suggestions what future research should focus on.

Keywords: contagious itch, atopic dermatitis, itch, mirror neurons, psychological factors

ITCH—A FREQUENTLY UNDERESTIMATED PHENOMENON

Everybody experiences itch in his or her life. Itch is a bodily sensation that is described as unpleasant and accompanied by the desire to scratch (Hafenreffer, 1660). It is a symptom that is considered to be rather annoying and bothersome (Dawn et al., 2009), but the subsequent scratching resulting in itch relief has been associated with positive feelings like pleasure (Mochizuki et al., 2014b).

Itch is a frequent symptom in the general population and among those with disease (Weisshaar and Matterne, 2014). About 8–17% of the general population (Dalgard et al., 2004; Matterne et al., 2009, 2011, 2013; Ständer et al., 2010) and up to 100% of patients with skin diseases like atopic dermatitis (AD) chronic idiopathic urticaria and psoriasis suffer from itch (Hanifin and Rajka, 1980; Yosipovitch et al., 2002; Reich et al., 2010). Pruritus has been documented in 10–70% of patients with kidney disease and 15–100% of patients with liver disease (Weisshaar and Dalgard, 2009).

In studies investigating the underlying physiological causes and consequences of itch, researchers generally use pruritogens like histamine, serotonin or cowhage to induce itch in both animals and humans (e.g., LaMotte et al., 2009; van Laarhoven et al., 2011; Papoiu et al., 2013). The application of pruritogens leads to intense feelings of itch and scratching behavior (Yamaguchi et al., 1999; Davidson et al., 2007). There is also a non-skin-manipulating method to induce itch by the presentation of certain sounds, pictures or videos. This method is referred to as audiovisual transmission of itch and is the basis of contagious itch.

AUDIOVISUAL TRANSMISSION OF ITCH IN HUMANS AND NONHUMAN PRIMATES

It can be easily acknowledged that people feel itch when they see another individual exhibiting scratching behavior or when they are discussing itch. However, this phenomena had not been studied until the last decade. The first study demonstrating that itch can be induced by visual stimuli was published by Niemeier et al. (2000). In this study, a human audience observed two slide-supported presentations. The first presentation was an itch-inducing lecture (including e.g., pictures of insects, scratch marks, allergic reactions) entitled, "itching—what is behind it?", while the second presentation focused on relaxation (including e.g., pictures on baby skin or children with their mothers). Analysis of the number of scratch movements during the presentations revealed a significant increase in scratching during the "itch lecture" compared to the "relaxation lecture". Moreover, questionnaire data revealed that increased itch was reported following the "itch lecture".

A decade later, a similar approach was used to analyze whether visual stimuli without auditory accompaniment would also be able to induce itch (Ogden and Zoukas, 2009). In this study, groups of students were shown video clips to induce coldness, pain or itch. The itch-inducing video contained pictures of head lice moving across hair strands and of people scratching their

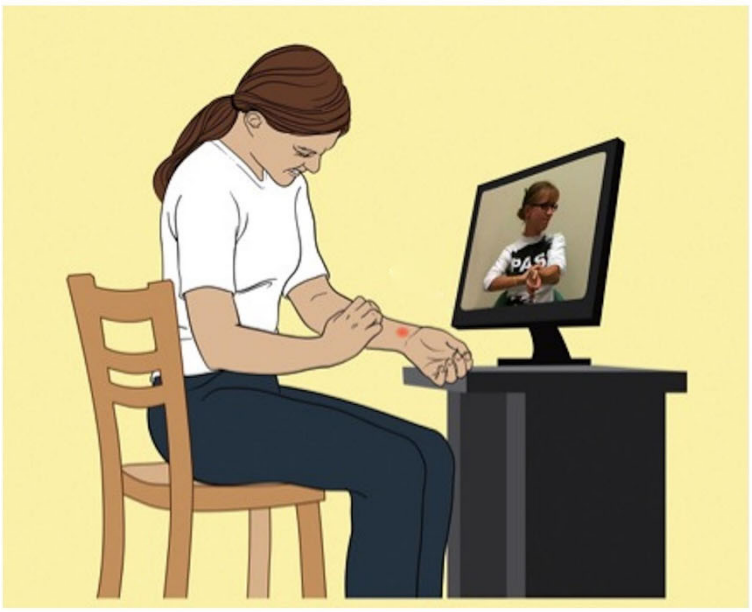

FIGURE 1 | Seeing another person scratching leads to a significant increase in scratching. This phenomenon is more pronounced in patients with chronic itch (patients with atopic dermatitis) compared to healthy controls (Modified picture from Papoiu et al., 2011).

heads. During the "itch video", the students not only scratched more often, but also reported higher levels of itchiness than during the videos on coldness and pain (Ogden and Zoukas, 2009). Unfortunately, this study lacked a control condition. It would have improved the study if scratch movements and itch intensity were recorded during a baseline situation, when subjects were presented with a "neutral video".

More recently, studies that included a control video provided further support that itch and scratching can be induced by visual itch stimuli. One investigation used videos showing other people scratching in order to induce itch in healthy humans and AD-patients (Papoiu et al., 2011). Both groups reported increased itch while watching short video clips of other people scratching (also see **Figure 1**) compared to watching a control video where the same people were sitting idle. However, the increase in itch intensity and in the number of scratch movements was significantly higher in AD-patients (Papoiu et al., 2011). Schut et al. (2014) were able to replicate the finding that patients suffering from AD are more prone to itch-inducing (audio-)visual stimuli than healthy controls.

It has also been shown that the body parts that are itchy due to visual stimuli differ between chronic itch patients and healthy controls. Papoiu et al. (2011) demonstrated that AD-patients scratched at body sites distal from the body part that was being scratched in the video, while healthy controls scratched body parts that were proximal to the body part that was being scratched in the video. Ward et al. (2013) supported this conclusion by maintaining that healthy participants preferentially scratch their heads (a proximal location), even when visual stimuli depict scratching of the chest and arms. Feneran et al. (2013) also demonstrated a similar pattern of macaque monkeys scratching parts of the body that were not identical to those attended to in neighboring scratching cagemates, as well as in videos of other monkeys scratching. This data suggests that contagious itch is not location-specific and a behavioral response that occurs in non-human primates and other mammals.

Rather than comparing the scratch and itch response between skin patients and healthy controls, Lloyd et al. (2013) were interested in the scratch- and itch response to *different* itch-related static images (e.g., insects or skin conditions) in healthy participants. The itch-related stimuli were delineated into the categories "skin contact" (e.g., ants crawling on a hand), "skin response" (e.g., scratching an insect bite) or "context only" (e.g., merely looking at insects). This study showed that the scratch responses increased the most, when subjects saw pictures of the "skin response" category, while the itch response was most intense to pictures showing itch stimuli of the category "context only" or "skin contact". The subjects were also asked to report how itchy they themselves felt, as well as how itchy they thought the subject

in the static image felt. Participants reported high itch sensations for both themselves as well as what they imagined the subjects in the pictures would feel, which may illustrate the role of empathy in contagious itch.

One of the candidates for empathic processing is the mirror neuron system (Iacoboni, 2009). The origin of this system is not fully understood yet: On the one hand it is argued that mirror neurons are inherent and serve to understand the actions of others, while on the other hand it is hypothesized that mirror neurons develop as a consequence of associative learning, which many times occurs in social interactions (Rizzolatti and Craighero, 2004; Hickok, 2009; Heyes, 2010). Mirror neurons were originally observed in the Ventral Premotor Area (VPA) of monkeys and are a specific type of motor cell that fires not only when the animal makes a specific movement, but also when it observes the same movement being carried out (di Pellegrino et al., 1992; Gallese et al., 1996; Iacoboni, 2009). Mirror neuron activation was also witnessed in macaque monkeys when they both performed a paper tearing hand action, as well as visualized and heard this hand action delivered (e.g., paper ripping). Control sounds, such as unrelated noise and monkey vocalizations, did not elicit VPA neuron firing (Kohler et al., 2002). However, mirror neurons are not only concerned with hand-controlled actions. In fact, Ferrari et al. (2003) have corroborated that mirror neurons also have jurisdiction over facial actions (e.g., biting, sucking). It is possible that this system may play a role in contagious itch, just as it is a possible neural mechanism in contagious yawning (Ikoma et al., 2006; Miller et al., 2012; Haker et al., 2013; Gallup and Eldakar, 2013). It still remains unclear if mirror neurons are actually activated during contagious itching. Therefore, this hypothesis should be investigated in future studies. Moreover, it would be interesting to explore whether it is an action-based mirror system or rather a feeling-based mirror system that is crucial for contagious itch. Regarding this question, Holle et al. (2012) argue that a feeling-based system has the more crucial role in contagious itch, due to the fact that the insula, a region associated with the affective components of bodily sensations, showed the more sustained activity during contagious itch. Supporting this idea, Papoiu et al. (2011) and Ward et al. (2013) have shown observers scratched body areas that differed in body locations than those they observed. Lloyd et al. (2013) demonstrated that viewing images of insects was able to induce more intense itch than viewing scratching behavior, which again emphasizes that it is not the action that is important to experience itch due to visual itch cues, but rather the negative affect that is evoked when seeing itch stimuli.

Another possible reason for contagious itch is classical conditioning. This is especially conceivable when even the simple visual presentation of itch inducing objects (e.g., ants, mosquito bites) become triggering factors of itch. According to the principle of classical conditioning (Pavlov, 2003), the pairing of an unconditioned stimulus (UCS; in this case e.g., the histamine release following a mosquito bite) with an originally neutral stimulus (NS; seeing the mosquito on the skin) can lead to a provocation of itch just from seeing the mosquito on the skin alone. In this scenario, the image of the mosquito has become a conditioned stimulus (CS). It would be interesting to test the hypothesis that contagious itch occurs due to classical conditioning processes in a study in which a pruritogen (e.g., histamine) is paired with a NS. After repeating the simultaneous presentation of these stimuli a few times, the originally NS should also be able to evoke itch and a scratch response by itself. A similar study design was used by Russell et al. (1984), who could show that histamine release can be "learned". Here, guinea pigs were first sensitized to bovine serum albumin (BSA), which acted as the UCS of histamine release. Afterwards, BSA together with a certain odor (fishy or sulfur) was injected in all guinea pigs. Moreover, as a control condition, saline was injected in combination with a different odor. The odor paired with histamine was counterbalanced between animals. After a few weeks, the plasma histamine concentration in response to the odor that was combined with histamine beforehand was higher than the histamine release due to the odor, which was given in the control condition. Similarly, Jordan and Whitlock (1972, 1974) were able to show that a scratch response could be conditioned in AD-patients and healthy controls. In these studies, a tone was used as the UCS, which was presented together with an itch stimulus (electrodes). Interestingly, in these studies, chronic itch patients reacted with a higher conditioned scratch response than healthy controls. This result is in line with the findings of two former studies, in which Papoiu et al. (2011) and Schut et al. (2014) found that visual itch cues, which in our opinion act as CS, also led to a higher scratch response in patients with chronic itch than in healthy controls.

Combining the approaches of classical conditioning and the activation of mirror neurons, Heyes (2010) proposes that mirror neurons are not hereditary, but rather a "byproduct" of associative learning. In the case of contagious itch, one could argue that because the pairing of itch and audiovisual cues (e.g., seeing a hand scratching or affected skin) has occurred much more frequently in chronic itch patients than in healthy controls, the mirror neurons firing during contagious itch should also be more active in chronic itch patients than in healthy controls. It would certainly be interesting to compare the activity of mirror neurons in patients with itchy skin diseases with their activity in healthy controls during contagious itch assuming that the presentation of visual itch stimuli would lead to higher mirror neuron activation in chronic itch patients than in healthy controls.

MOOD AND PERSONALITY AS MODERATORS OF AUDIO-VISUALLY TRANSMITTED ITCH

Whether one is susceptible to audiovisual itch stimuli also depends on personality characteristics and on the person's mood. Ogden and Zoukas (2009) found a significant positive correlation between itch and anxiety. The more the students felt itchy after watching an itch inducing video, the more they also reported to experience anxiety. Of course, this relationship does not conclude whether anxiety precedes or follows itch. It only suggests that there is a correlation between psychological states and clinical symptoms, which is an interesting finding in itself.

Neuroticism (defined as emotional instability) is a personality trait that has been shown to be associated with the itch intensity induced by visual stimuli in healthy participants (Holle et al.,

2012). Persons, who are neurotic, are more prone to experience negative emotions like fear, anger, disgust and embarrassment (McCrae and Costa, 2010). Holle et al. (2012) found a significant positive relationship between this trait and the itch increase due to watching another person scratching. Though this relationship was only investigated in healthy participants, but not in patients suffering from chronic itch.

The relationship between visually transmitted itch and psychological variables was further strengthened by a study in which depression and other personality characteristics were shown to be significant predictors of the extent of self-reported induced itch in AD-patients (Schut et al., 2014). AD-patients who reported personality traits of not being cooperative (low agreeableness) and at the same time high scores on the scale "public self-consciousness", showed a higher number of scratch movements than patients who did not show this psychological phenotype (Schut et al., 2014). Interestingly, this relationship could only be shown in AD-patients, but not in healthy controls (Schut et al., 2014).

Although these findings suggest a relationship between negative mood, personality characteristics and an increase in itch/scratching, we cannot assume that persons with a certain personality will definitely develop an itchy skin disease. It is important to point out that there are many factors contributing to the development and maintenance of a disease. A specific combination of personality characteristics and moods should only be seen as one factor that can aggravate the experience of itch in an experimental setting.

NEXT STEPS IN THE RESEARCH ON VISUALLY TRANSMITTED ITCH

There are still many open questions in the research of contagious itch. Although there are initial hypotheses as to why people feel an itch sensation when they observe the scratching behavior of others, these theories need to be further tested and verified. One explanation of contagious itch was presented by Niemeier et al. (2000), who postulated that itch-inducing stimuli may stimulate histamine release (Niemeier et al., 2000). Yet, it can also be assumed that contagious itch is actually a brain-phenomenon leading "only" to brain activation of certain interoceptive brain areas (e.g., the insula), and that no pruritogens are released.

Additional, functional brain imaging studies investigating brain substrates involved in contagious itch in healthy and chronic itch patients during audiovisually induced itch are rare (Mochizuki et al., 2014a) and therefore required. Mochizuki et al. (2013) displayed pictures of itch-related situations (e.g., mosquito bite; skin diseases) to subjects who underwent FMRI scans and were asked to simultaneously internally focus on their own analogous body parts. The pictures led to significantly higher brain activity in the left prefrontal cortex, left fusiform gyrus, bilateral anterior insular cortex, left orbitofrontal cortex, left supplementary motor area, left striatum, bilateral thalamus and bilateral cerebellum, as well as to significantly greater feelings of itch compared to control pictures showing unaffected skin. Holle et al. (2012) could show that the thalamus, primary somatosensory cortex, premotor cortex and insula were activated while watching videos of other people scratching. Even though these two studies give preliminary insight into which brain areas are activated when experiencing contagious itch, they only included healthy controls and it is unclear whether the same brain areas would be activated in chronic itch patients. It is reasonable to assume that contagious itch evokes a greater negative emotional response in chronic itch patients than in healthy controls, which might lead to a greater activation of the limbic system. Moreover, we would assume the insular and anterior cingulate cortices to be more activated in patients with chronic itch, because activation in these brain areas was associated with empathy for other bodily sensations like pain and touch (Bufalari and Ionta, 2013). Empathy for the other person scratching should be more pronounced in patients suffering from chronic itch compared to healthy controls. This hypothesis should be investigated in future studies.

Other important areas to investigate are whether demographic variables like age and gender have an effect on this behavioral phenomenon. Because neuroticism is more pronounced in younger than in older adults (McCrae et al., 1999) and is associated with contagious itch (Holle et al., 2012), it would also be reasonable to assume that younger subjects are more susceptible to contagious itch. Also, we hypothesize that due to higher empathy (e.g., Wilson et al., 2012), women may be more susceptible to visual itch cues. It has already been shown that women report higher itch intensities than men on visual analog scales (Ständer et al., 2013).

Another meaningful next step in the field of contagious itch is to investigate the effectiveness of strategies or treatments on reducing itch intensity due to visual itch cues. One possible method to diminish contagious itch is to prevent patients with itchy skin diseases from sharing a room with each other in the hospital. Another idea would be to extinct the classically conditioned response of scratching by pairing the visual itch cue with an itch-relieving cue. For instance, an itch-inducing image could be paired with that of a soothing skin ointment. Another psychological approach might be to lower the induced scratch response by teaching habit reversal techniques (Azrin and Nunn, 1973; Rosenbaum and Ayllon, 1981; Melin et al., 1986; Norén and Melin, 1989), which patients could then perform when being exposed to itch stimuli or to reduce stress during exposure to visual itch cues by e.g., the practice of relaxation techniques like progressive muscle relaxation (Jacobson, 2011).

CONCLUSION

Contagious itch is a common behavioral phenomenon that evokes unique brain activations. More research is required to understand the neural substrates involved in contagious itch.

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