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DISSERTATION

Medizinethische Untersuchung innovativer Therapien für schwere psychiatrische Erkrankungen

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Abkürzungsverzeichnis:

AN: Anorexia nervosa

ME: Milde Enzephalitis

THS: Tiefe Hirnstimulation

BMI: Body Mass Index

1. Zusammenfassung (Deutsch)

Einleitung: Anorexia nervosa und Schizophrenie sind schwere psychische Erkrankungen, welche oft einen chronischen Verlauf nehmen, von weiteren psychischen und somatischen Erkrankungen begleitet werden und mit einer hohen Suizidrate einhergehen. Das Verständnis psychischer Erkrankungen basiert heutzutage auf einem bio-psychosozialen Krankheitsmodell, unterstützt durch Erkenntnisse aus Genetik, Neuroimaging, Molekularbiologie und der kognitiven Neurowissenschaft.
Methodik: Die vorliegenden Publikationen sollen am Beispiel neuartiger, kontrovers diskutierter Therapiemethoden der Frage nachgehen, wie biologisch orientierte Therapieansätze für psychische Erkrankungen ethisch zu bewerten sind. Behandelt wird der Einsatz (A) psychiatrischer Neurochirurgie (*THS*, Radiochirurgie und ablative stereotaktische Neurochirurgie) bei Anorexia nervosa und (B) antientzündliche Therapien (entzündungshemmende Medikamente, Immuntherapien) für Schizophrenie. Die medizinethische Analyse erfolgt, nach einer umfassenden Auswertung der Fachliteratur, nach den medizinethischen Prinzipien von Beauchamp und Childress.
Ergebnisse: Ein biomedizinisches Verständnis psychischer Erkrankungen kann die Entwicklung effektiver Therapien fördern. Es stellt die Herausforderung, etablierte Diagnosesysteme zu revidieren, eine nötige Zusammenarbeit psychiatrischer und somatischer Disziplinen zu fördern und dadurch einen ganzheitlichen Blick auf die menschliche Gesundheit zu werfen. Andererseits zeigt die empirische Forschung, dass ein biomedizinisches Verständnis psychischer Erkrankungen – anders als vielfach erwartet – die Stigmatisierung und Diskriminierung psychischer Krankheiten verstärkt und zur Vernachlässigung sozialer Krankheitsursachen führt.

2. Abstract (English)

Introduction: Both Anorexia nervosa and Schizophrenia are severe and often chronic mental disorders. They are accompanied by additional mental and somatic diseases and by a high suicide rate. Currently, models of mental illness are based on a bio-psychosocial understanding, supported by genetics, neuroimaging, molecular biology, and cognitive sciences.

Methods: The publications presented evaluate biologically-oriented therapies for mental disorders ethically, using the examples of (A) psychiatric neurosurgery (including deep brain stimulation, radiosurgery and ablative neurosurgery) as therapeutic intervention for anorexia nervosa, and (B) anti-inflammatory therapies (including anti-inflammatory medication, immunotherapies) in the treatment of schizophrenia. The ethical analysis is based on the „Principles of Biomedical Ethics“ of Beauchamp and Childress following a comprehensive analysis of the recent medical literature.

Results: Biomedical interpretations of mental disorders can positively contribute to the development of effective therapies. Biological interpretations challenge established diagnostic systems and encourage an interdisciplinary therapeutic approach. However, empiric research indicates that a biological interpretation, contrary to expectation, is closely tied to increased stigmatization and discrimination and may lead to a neglect of social causes of mental illness.

3. Einführung

3.1. Psychiatrische Neurochirurgie (Publikation 1 und Publikation 2)

Nachdem in den 1970er Jahren von der „Psychochirurgie“ Abstand genommen wurde — Gründe waren die häufig schweren Komplikationen und ein unethischer Einsatz der Verfahren — erleben neurochirurgische Eingriffe in der Behandlung psychiatrischer und psychosomatischer Erkrankungen in den letzten Jahren ein Comeback [1] [2]. Die moderne psychiatrische Neurochirurgie beinhaltet unter anderem folgende Verfahren: Tiefe Hirnstimulation (*THS*), ablative neurochirurgische Verfahren (stereotaktische Mikrochirurgie via mechanischer Durchtrennung oder Thermokoagulation), und radiochirurgische Interventionen (Gamma Knife, CyberKnife) [3]. Diese durch Neuroimaging gestützten Techniken, gewährleisten heutzutage mehr Sicherheit und therapeutische Effektivität [3] [4] [5]. Medizinisch betrachtet ist keines der Verfahren einem anderen überlegen. Sie haben ein jeweils unterschiedliches Risiko- und Nutzenprofil. Ein Beispiel für den Einsatz neurochirurgischer Verfahren bei psychischen Erkrankungen ist Anorexia nervosa (*AN*) [2] [6]. Hier zeigten bildgebende Studien der letzten Jahre Veränderungen auf der Ebene von Neurotransmittern bis hin zu ganzen Hirnarealen, weshalb neurochirurgische Eingriffe als therapeutische Möglichkeit in Betracht gezogen werden [2] [5]. Während psychiatrische *THS* intensiv von Medizinethikern diskutiert wurde, ist eine ethische Diskussion von ablativen Verfahren und Radiochirurgie, trotz zunehmendem Einsatz in der Psychiatrie, bisher kaum zu finden [7] [8].

3.2. Milde-Enzephalitis-Hypothese der Schizophrenie (Publikation 3 und Publikation 4)

Bereits seit der Influenza-Pandemie im Jahre 1918 wurde über post-Influenza-Psychosen berichtet und ein Zusammenhang zwischen Infektionen und psychotischen Krankheitsbildern vermutet [9]. Aktuell ist dieser Ansatz wieder Gegenstand eines zunehmend aufblühenden Forschungsgebietes, welches sich mit entzündlichen Prozessen und der Rolle des Immunsystems bei schweren psychiatrischen Erkrankungen befasst [10] [11] [12] [13] [14] [15]. Hierzu gehört die Milde-Enzephalitis *(ME)*-Hypothese der Schizophrenie, welche Karl Bechter erstmals im Jahr 2001 publizierte [16], und die seitdem kontinuierlich aktualisiert wird [17] [18] [19]. Der *ME*-Hypothese zufolge leidet eine relevante Untergruppe der Schizophrenie-PatientInnen an einer milden, aber chronischen Form von Enzephalitis, welche z.B. durch Virusinfektionen, Hirntraumata oder Autoim-

munkrankheiten ausgelöst wird [9] [11] [18]. Milde Enzephalitis zeichnet sich durch einen Zustand geringgradiger Neuroinflammation mitsamt molekularen und zellulären Veränderungen aus (*Low-Level Neuroinflammation*). Diese Veränderungen sind am sensitivsten mittels Liquoranalyse, Serummarkern und Neuroimaging zu entdecken [12] [18]. Dieser vielversprechende Forschungsansatz legt die Grundlage für neue, seit langem benötigte Therapien [10] [11] [13] [14]. Eine Untersuchung der erwartbaren Konsequenzen, welche mit der Forschung um die *ME*-Hypothese einhergehen, sowie deren ethische Diskussion, ist — trotz unmittelbarer Relevanz für PatientInnen, ForscherInnen und TherapeutInnen — in der Literatur bislang noch nicht zu finden

4. Fragestellung

Die vier Publikationen untersuchen die Frage, wie zwei neue, biologisch orientierte Therapieansätze in der Psychiatrie ethisch zu bewerten sind: (A) Psychiatrische Neurochirurgie, insbesondere bei Anorexia nervosa und (B) anti-inflammatorische Therapien basierend auf der Milde-Enzephalitis-Hypothese der Schizophrenie.

5. Medizinethische Methodik

5.1. Prinzipien der biomedizinischen Ethik nach Beauchamp und Childress

Die medizinethische Erörterung der Publikationen basiert auf dem Buch „Principles of Biomedical Ethics“ von Beauchamp und Childress, das man als Standardwerk der modernen Medizinethik ansehen kann [20]. Die von Beauchamp und Childress aufgestellten vier Prinzipien können als Ausgangspunkt für die systematische Analyse ethischer Probleme in Klinik und medizinischer Forschung dienen. Eine Hierarchie der Prinzipien wird dabei explizit verneint. Daher lassen sich aus diesem Ansatz häufig keine definitiven Konfliktlösungen ableiten. Diese müssen auf Basis der spezifischen Eigenschaften des Falles sowie der moralischen Überzeugungen der beteiligten Personen herausgearbeitet werden [21]. In der modernen Medizinethik hat sich jedoch eine Vorrangstellung des Prinzips *Respekt vor der Autonomie* etabliert [22]. Die vier Prinzipien werden im Folgenden kurz dargestellt.

Prinzip des Respekts vor der Autonomie (*engl. respect for autonomy*)

PatientInnen haben ein Recht auf Selbstbestimmung über medizinische Behandlungen. Frei von äußeren Zwängen und Manipulationen durch Dritte sollen sie Entscheidungen über Diagnostik und Therapien nach eigenen Wünschen, Werten und Zielen treffen. ÄrztInnen sollen die PatientInnen durch adäquate Aufklärung soweit unterstützen, dass diese eigenständige Entscheidungen treffen können (*positive Verpflichtung*). Einige AutorInnen vertreten die Auffassung, dass im Falle einer krankheitsbedingt eingeschränkten Autonomiefähigkeit, diese — sofern möglich — ärztlich wiederherzustellen ist [22] [23]. Die Entscheidung gegen eine Behandlung ist zu respektieren, sofern diese Entscheidung frei getroffen wurde (*negative Verpflichtung*). Einen besonderen Stellenwert nimmt das *informierte Einverständnis* ein (*engl.: informed consent*): Nach Aufklärung über geplante Untersuchungen, Therapien sowie mögliche Alternativen müssen PatientInnen ihr explizites Einverständnis geben, damit eine Behandlung rechtlich zulässig ist. Für eine rechtswirksame Einwilligung sind einige Voraussetzungen notwendig: ausreichende Aufklärung, Verständnis der Aufklärung, freiwillige Entscheidung und Entscheidungskompetenz der PatientInnen (Einwilligungsfähigkeit). Gerade bei PatientInnen mit aktuell schweren psychiatrischen Erkrankungen ist die Einwilligungsfähigkeit häufig nicht gegeben.

Prinzip der Fürsorge (*engl. beneficence*)

Das Prinzip der Fürsorge beschreibt das Streben nach dem Wohl der PatientInnen, welches durch aktives Handeln (Therapie, Prävention, Palliation) erreicht werden soll. Dieses Prinzip tritt gelegentlich in Konkurrenz mit dem *Autonomieprinzip*, nämlich dann, wenn PatientInnen Behandlungen ablehnen, die von behandelnden ÄrztInnen als notwendig für das gesundheitliche Wohl angesehen werden. Eine Missachtung der *Patientenautonomie* liegt vor, wenn die Entscheidung der einwilligungsfähigen und selbstbestimmten PatientIn übergangen wird (*harter Paternalismus*). Wird der Patientenwille mit guten Gründen als unfrei bzw. nicht selbstbestimmt betrachtet (z.B. aufgrund einer akuten Psychose oder schwerer Demenz) und zugunsten einer Benefizienz-orientierten Entscheidung oder zur Wiederherstellung der Autonomiefähigkeit missachtet, spricht man von *weichem Paternalismus*.

Prinzip des Nicht-Schadens / Schadensvermeidung (*engl. non-maleficence*)

Dieses Prinzip geht auf das hippokratische Prinzip zurück, PatientInnen durch Eingriffe primär nicht zu schaden (*„primum nil nocere“*), und soll ÄrztInnen von risikoreichen und unerprobten Behandlungen abhalten. Häufig gerät es mit dem *Prinzip der Fürsorge* in Konflikt, da jede Therapie mit Nebenwirkungen und Risiken verbunden ist. Umso wichtiger ist ein sorgfältiges Abwägen von Nutzen und Schaden (*Nutzen-Risiko-Analyse*).

Prinzip der Gerechtigkeit (*engl. justice*)

Gesundheitsleistungen und -belastungen (z.B. finanzielle Mittel, Behandlungen, Kosten, Risiken bei wissenschaftlichen Studien) sollen gerecht verteilt werden.

Über Gerechtigkeit gibt es unterschiedliche Auffassungen, aus denen sich in konkreten Fragen ganz unterschiedliche Schlussfolgerungen ergeben können. Beauchamp und Childress diskutieren die folgenden Gerechtigkeitstheorien: 1. *Utilitaristisch*: jedem das, was den gesellschaftlichen Nutzen maximal fördert; 2. *Libertär*: für jeden ein Maximum an Freiheit und Eigentum, resultierend aus der Ausübung von Freiheitsrechten und der Teilnahme am freien Markt; 3. *Kommunitarisch*: für jeden so viel wie gemäß den Regeln einer fairen Verteilung in moralischen Gemeinschaften angemessen; 4. *Egalitär*: für jeden das gleiche Maß an Freiheit und gleicher Zugang zu notwendigen und wertvollen Gütern; 5. *Befähigungsbasiert*: für jeden so viel wie nötig, um die Fähigkeiten, die für ein gelingendes Leben notwendig sind, auszuüben; 6. *Grundlage für Wohlergehen*: für jeden so viel, dass die Mittel für die Kerndimensionen des Wohlergehens vorhanden sind.

5.2. Ethische Problematik iatrogener Persönlichkeitsveränderungen

Die Diskussion über Persönlichkeitsveränderungen in *Publikation 2* befasst sich mit ethischen Aspekten im Zusammenhang mit iatrogenen Persönlichkeitsveränderungen. Sie ist gestützt auf Arbeiten von Müller und Christen [24], und Müller [25].

6. Ergebnisse: Ethische Aspekte psychiatrischer Neurochirurgie

6.1. „Rivaling paradigms in psychiatric neurosurgery: adjustability versus quick fix versus minimal-invasiveness“ (Publikation 1)

6.1.1. Methodik

Auf Grundlage einer Auswertung der Fachliteratur werden die Verfahren der psychiatrischen Neurochirurgie (*THS*, mikrochirurgische Ablation und Radiochirurgie) einander gegenübergestellt und hinsichtlich der folgenden Kriterien verglichen: 1. Modulierbarkeit; 2. Verschiedene Zielregionen zugleich behandelbar; 3. Reversibilität; 4. Notwendigkeit einer Kraniotomie; 5. Zeitdauer bis zum Wirkeintritt; 6. Zeit und Aufwand der Behandlung, Behandlungshäufigkeit; 7. Kosten der Behandlung; 8. Kurz- und Langzeitrisiken/-folgen; 9. Mögliche Nebenwirkungen; 10. Nachteilige Folgen im täglichen Leben (z.B. Flughafenscanner); 11. Nachteilige Folgen für weitere medizinische Behandlungen/Diagnostik (z.B. MRT); 12. Psychosoziale Auswirkungen der Behandlung.

6.1.2. Ergebnisse

THS kann für PatientInnen, die großen Wert auf *Modulierbarkeit* und (relative) *Reversibilität* legen, eine passende Wahl sein [1] [6]. Allerdings ist diese Eigenschaft ambivalent, da sie zu Manipulations- und Entfremdungsgefühlen führen kann [8]. PatientInnen, die einen schnellen Wirkeintritt wünschen oder brauchen, finden in *ablativer Mikrochirurgie* im Sinne eines „*Quick fix*“ ein gutes Instrument [7] [8]. Dagegen sind für PatientInnen, die sich keiner Operation und Anästhesie unterziehen können oder wollen, *radiochirurgische Interventionen* geeignet, insbesondere aufgrund der niedrigen Rate an Nebenwirkungen (Paradigma „*minimal-invasiv*“) [1] [26]. Ablative Mikrochirurgie und Radiochirurgie sind vor allem für PatientInnen, die nicht an regelmäßigen Nachbehandlungen oder Kontrollen teilnehmen können, für diejenigen mit begrenztem Budget oder fehlendem Versicherungsschutz eine Alternative (keine Langzeitkosten) [1] [6].
Welches Verfahren bei einem individuellen Patienten am besten geeignet ist, lässt sich daher nicht allgemein sagen. Vielmehr müssen auch individuell unterschiedliche Präferenzen, Wertvorstellungen und Lebenssituationen der PatientInnen sowie die Art der Erkrankung und der allgemeine Gesundheitszustand berücksichtigt werden.

6.2. „An Ethical Evaluation of Stereotactic Neurosurgery for Anorexia Nervosa“ (Publikation 2)

6.2.1. Methodik

Für den Review zu stereotaktischen Verfahren zur Behandlung der *AN* wurden im Juni 2014 jeweils zwei Suchen in PubMed (PubMed, National Library of Medicine, Washington) und im Web of Science, Core Collection, durchgeführt. Durch Kombination des Schlagwortes „Deep Brain Stimulation“ oder „DBS“, jeweils mit den Suchkriterien „Anorexia“, oder „Eating Disorder*“, wurden Studien und Fallberichte gesucht, die zwischen 1990 und 2014 publiziert worden waren. Für die Suche nach ablativen Verfahren kombinierten wir die Operatoren „(stereotactic* OR ablat* OR functional neurosurg* OR capsulotomy OR cingulotomy)“ mit „Anorexia“ oder „Eating Disorder*“. Zudem wurden die Referenzlisten der gefundenen Artikel sowie der einschlägigen Publikationen gesichtet. Dies ergab 45 Publikationen zu *THS* und 76 zu ablativen Verfahren. Nach Anwendung der Ausschlusskriterien (Aufsätze zu Tumor-assoziierter Anorexie, *THS* bei PatientInnen mit Parkinson, Studien mit Tieren/Tierversuche, Reviews, Kommentare, Leitartikel, bioethische Artikel) konnten vier Studien und zwei Fallberichte zu *THS*, und eine Studie und zwei Fallberichte zu ablativen Verfahren bei *AN* in den Review einbezogen werden.

Die ethische Analyse der Ergebnisse aus dem Review basiert auf den *Prinzipien der biomedizinischen Ethik* [20]. Die Diskussion über iatrogene Persönlichkeitsveränderungen stützt sich auf Arbeiten von Müller und Christen [24], und Müller [25].

6.2.2. Ergebnisse

a) Review: Eine detaillierte Zusammenstellung der Ergebnisse kann den Tabellen auf Seite 36 und 37, sowie Seite 39-41 entnommen werden. Zusammenfassend wurden zwischen 1990 und 2014 27 PatientInnen mit *AN* neurochirurgisch behandelt: 18 mittels *THS* [27] [28] [29] [30] [31] [32] und neun mit ablativen Verfahren [33] [34] [30]. Das Alter der PatientInnen lag zwischen 16 und 57 Jahren. Alle hatten neben *AN* psychiatrische Begleiterkrankungen, welche sich postoperativ bei 25 von 27 besserten (Näheres siehe Tabelle 2 auf Seite 39-41). Die Body Mass Index (*BMI*)-Werte lagen präoperativ zwischen 9,1 und 18,5 kg/m^2. Postoperativ verbesserten sich die *BMI*-Werte bei 23 von 27 PatientInnen, während sie sich bei vier von 27 (*THS*-PatientInnen) verschlechterten

[29]. Die Erkrankungsdauer betrug zwischen einem Jahr und 39 Jahren. Zielstrukturen bei *THS* waren der Nucleus accumbens [30] [31] [32], das subcallosale Gyrus Cinguli (subcallosal cingulum) [27] [29], die ventrale Capsula/das ventrale Striatum (ventral capsula/ventral striatum) [28]. Bei den ablativen Verfahren wurden dorsomediale Thalamotomie [33], bilaterale anteriore Kapsulotomie durch Thermokoagulation [34] und Radiofrequenzablation des Nucleus accumbens [30] durchgeführt.
Während es einige schwerwiegende Nebenwirkungen bei *THS* gab (intraoperative Panikattacke, kardiale Luftembolie, epileptischer Anfall, Pankreatitis, Refeeding-Syndrom) [29], wird bei den ablativen Verfahren nur von leichten und vorübergehenden Nebenwirkungen berichtet (z.B. Orientierungs- und Konzentrationsstörungen, Kopfschmerzen) [30] [34]. Vier von sechs Publikationen zu *THS* und eine von drei Publikationen zu ablativen Verfahren gehen allerdings nicht auf Nebenwirkungen ein [27] [28] [31] [32] [33].

b) Ethische Analyse: Aus den Ergebnissen des Reviews ergeben sich fundamentale ethische Fragen:

1. Obwohl psychosoziale Faktoren am Beginn der Erkrankung beteiligt sind, ist dies ethisch betrachtet kein Argument für eine pauschale Absage an neurochirurgische Interventionen: Ähnlich wie bei Suchterkrankungen ist es für PatientInnen mit *AN* sehr schwer möglich, aus eigener Kraft das selbstzerstörerische Verhalten zu unterbinden, auch wenn dieses Verhalten am Anfang selbstbestimmt gewesen sein mag [35].
2. Anhand der vorliegenden Daten kann keine klare *Nutzen-Risiko-Analyse* für die verschiedenen neurochirurgischen Verfahren erstellt werden, da Nebenwirkungen lückenhaft publiziert wurden und dieses Gebiet einen Publikationsbias hat [2] [4] [36]. Für ablative Verfahren ist das *Nutzen-Risiko-Verhältnis* auf der Grundlage der publizierten Literatur – unter Vorbehalt – positiv zu bewerten.
3. Die Wahrung der *Patientenautonomie* inklusive *informiertem Einverständnis* ist im Falle der *AN* schwierig: a) Die Informationslage über Nutzen und Risiken der neuen Therapiemethoden ist ungenügend, dementsprechend kann nur eingeschränkt aufgeklärt werden. b) Die Einwilligung in einen neurochirurgischen Eingriff geschieht möglicherweise aus Verzweiflung und falschen Hoffnungen [6] [37] [38]. c) Die Einwilligungsfähigkeit kann krankheitsbedingt eingeschränkt sein [6].
4. Ethisch besonders problematisch ist der Einsatz von psychiatrischer Neurochirurgie bei Minderjährigen [6] [38]: a) Ältere Kinder und Jugendliche sind weder voll kompetent,

noch voll inkompetent in ihrer Entscheidungsfindung [23]. b) Langzeiteffekte und -auswirkungen von Eingriffen in Gehirne, welche sich noch in der Entwicklung befinden, sind ethisch besonders bedenklich [38]. c) Ethisch unter keinen Umständen vertretbar sind neurochirurgische Zwangseingriffe gegen den Willen des Kindes bzw. Jugendlichen [6] [39].

5. Der Einsatz von neurochirurgischen Therapien ist ethisch nur dann gerechtfertigt, wenn weniger invasive und risikoreiche, Leitlinien-basierte Therapien keinen signifikanten Nutzen bringen [5] [6] [38]. Allerdings ergab unsere Analyse der publizierten Daten, dass einige der PatientInnen präoperativ evidenzbasierte Therapien nicht erhalten hatten und/oder die Krankheitsdauer zu kurz war, um von Therapieresistenz ausgehen zu können [2] [37].

6. Die Vielfalt der Methoden und Zielstrukturen, die in der neurochirurgischen Behandlung der *AN* Anwendung finden, basiert auf unterschiedlichen Paradigmen zu *AN.* Die unterschiedlichen Verfahren und Zielstrukturen wurden in der Vergangenheit bereits für die Behandlung von anderen psychiatrischen Krankheitsbildern verwendet [37] [40]. Anhand der momentanen Studienlage lässt sich keine klare Aussage zu den am besten geeigneten Zielgebieten für die Behandlung verschiedener psychiatrischer Erkrankungen treffen [4] [41] [42]. Gerade die psychiatrische Neurochirurgie braucht jedoch eine gute wissenschaftliche Basis, um invasive Behandlungen mit hohen Komplikationsrisiken an vulnerablen PatientInnen rechtfertigen zu können [2] [6] [37].

7. Ergebnisse: Ethische Aspekte der Milde-Enzephalitis-Hypothese der Schizophrenie *(Publikation 3 und Publikation 4)*

7.1. Methodik

Publikation 3 (*„Ethical Implications of the Mild Encephalitis Hypothesis of Schizophrenia“*) und *Publikation 4* (*„How will the Mild Encephalitis Hypothesis of Schizophrenia influence Stigmatization?“*) untersuchen, mit Hilfe der *Prinzipien der biomedizinischen Ethik* [20] und basierend auf der aktuellen empirischen Literatur, welche individuellen und gesellschaftlichen Veränderungen mit der Bestätigung der Milde-Enzephalitis-Hypothese zu erwarten wären, und wie diese potentiellen Folgen ethisch zu bewerten sind. *Publikation 3* befasst sich mit den Folgen für Diagnostik, Therapie und Versorgung der betroffenen PatientInnen sowie mit den zu erwartenden Auswirkungen auf die medizinisch-pharmazeutische Forschung, die Gesetzgebung und Rechtsprechung zu Zwangsbehandlungen. In *Publikation 4* liegt der Fokus auf den zu erwartenden Auswirkungen der *ME*-Hypothese auf die Stigmatisierung von Schizophrenie-PatientInnen.

7.2. Ergebnisse

Die empirische Bestätigung der *ME*-Hypothese hätte zur Folge, dass Schizophrenie nicht länger als unheilbare, chronische Krankheit mit zunehmender Behinderung und sozialer Ausgrenzung betrachtet werden würde. Schizophrenie wäre vielmehr eine häufig heilbare, neurologische Erkrankung. Dieser Paradigmenwechsel hätte u. E. weitreichende Konsequenzen:

1. Ein derart somatisch orientierter Blick auf psychische Krankheiten fordert aktuelle psychiatrische Klassifikationssysteme (DSM-5, ICD-10) heraus, in denen psychische Krankheiten deskriptiv anhand ihrer Symptome diagnostiziert werden [43]. „Schizophrenie“ stellt hier einen Sammelbegriff für ein klinisches Bild dar, dessen Ätiopathogenese ganz unterschiedlich sein kann [43] [44]. Um biomedizinische Subtypen psychotischer Erkrankungen zu identifizieren (*„deconstructing schizophrenia“*) muss dieser rein symptomorientierte Blick aufgegeben werden [44] [45].
2. Aus der *ME*-Hypothese folgt, dass die Diagnostik und Behandlung von Schizophrenie-PatientInnen multidisziplinär durch PsychiaterInnen und NeurologInnen, und ggf. weitere Fachdisziplinen aus der Inneren Medizin erfolgen sollte [15] [18]. Dies beinhaltet, dass zusätzlich zu ICD-10 oder DSM-5 eine sorgfältige Differentialdiagnostik mit biomedizinischen Tests (gepaarte Liquor-Serum-Untersuchung, MRT, EEG) gleich zu

Erkrankungsbeginn erfolgen sollte, um somatische Ursachen frühzeitig erkennen und individuell behandeln zu können (z.B. Milde Enzephalitis, Autoimmun-Enzephalitis) [12] [13] [15] [19].
3. Qualitativ hochwertige Studien und systematische Reviews zeigen vor allem bei Ersterkrankten mit Schizophrenie eine Wirksamkeit entzündungshemmender Medikamente (z.B. N-acetyl-cystein, Aspirin, Vitamin C) [11] [14] [46]. Sollten künftige Studien bestätigen, dass ein Teil der Schizophrenie-PatientInnen an Milder Enzephalitis leidet, welche sich unter anti-inflammatorischer Medikation bessert, sollte das Therapieregime künftig Wirkstoffe beinhalten, die diese Entzündung bekämpfen.
4. Diese Entwicklung hat Auswirkungen auf die Pharmaindustrie: Antipsychotika könnten ggf. durch entzündungshemmende Medikamente ergänzt oder ersetzt werden. Dies würde der Pharmaindustrie Umsatzverluste einbringen, während andererseits der Bedarf an (neuen) entzündungshemmenden Medikamenten steigen würde [13] [14].
5. Die höchstrichterliche Rechtsprechung bezüglich medikamentöser Zwangsbehandlung könnte sich mit der Entwicklung kausaler, nebenwirkungsarmer Medikamente ändern: Zwangsbehandlungen wären wahrscheinlich leichter genehmigungsfähig, jedoch aufgrund einer zunehmenden Patienten-Compliance und besseren Wirksamkeit der Medikamente seltener erforderlich.
6. Gesellschaftlich betrachtet kann die *ME*-Hypothese zur besseren Wiedereingliederung der PatientInnen und zur Entstigmatisierung von Schizophrenie beitragen, sofern sie zu erfolgreichen Therapiemöglichkeiten und einer Reduktion der langfristigen Behinderungen führt.

Der Aspekt der Entstigmatisierung wird in *Publikation 4* näher untersucht:
1. Bessere Wiedereingliederung gelingt durch die Kombination aus effektiven Medikamenten, die die PatientInnen wieder aktiv am gesellschaftlichen Leben teilhaben lassen und zum anderen dadurch, dass Betroffene als weniger bedrohlich wahrgenommen werden [43] [47].
2. Die *ME*-Hypothese kann entstigmatisierend wirken, indem sie die PatientInnen von der Verantwortung bzw. Schuld für die Erkrankung entbindet (keine *Onset-Verantwortung*). Der *attribution theory* zufolge ist die Zuschreibung von Schuld für eine Erkrankung ein wesentlicher Faktor für die Stigmatisierung [47] [48]. Milde Enzephalitis kann durch Infektionen getriggert werden, was veranschaulicht, dass es jeden treffen kann.

3. Ein multidisziplinärer Ansatz bei Diagnostik und Therapie, welcher aus der *ME*-Hypothese folgt, könnte helfen, die PatientInnen aus dem hochstigmatisierten Feld der „Geisteskranken“ herauszulösen [43].
4. Rein genetische Erklärungen psychischer Erkrankungen verstärken die Stigmatisierung, da damit eine unveränderbare, schwerwiegende und erbliche Eigenschaft betont wird (*genetischer Determinismus*) [47] [48] [49]. Dahingegen kann eine Betonung biologischer Faktoren (Infektion, Autoimmunität) zusammen mit einer genetischen Vulnerabilität entstigmatisierend wirken.

8. Diskussion

8.1. Vergleich der untersuchten Therapiemethoden

Die beiden hier untersuchten Therapiemethoden, (A) psychiatrische Neurochirurgie, (B) entzündungshemmende Medikamente, sind für die Behandlung schwerer psychiatrischer Erkrankungen vorgesehen. Ursprünglich aus der neurologischen Forschung und Therapie stammend, basieren sie auf einem somatischen Konzept psychischer Krankheit und stehen damit im Widerspruch zu psychologischen und sozialen Konzepten.

Die beiden Therapiemethoden unterscheiden sich darin, dass es sich bei neurochirurgischen Interventionen um direkte, operative Eingriffe in das Gehirn handelt; Hirnstrukturen werden reversibel durch elektrischen Strom deaktiviert oder stimuliert (*THS*) oder irreversibel läsioniert (ablative Mikrochirurgie und Radiochirurgie). Dagegen kommen im Rahmen der *ME*-Hypothese überwiegend medikamentöse Interventionen (entzündungshemmende Medikamente) zum Einsatz. Die psychiatrische Neurochirurgie beinhaltet damit Verfahren, welche invasiv und teuer sind [1] [25] [38], während mit der *ME*-Hypothese bekannte Medikamente eingesetzt werden, die einfach verfügbar und preiswert sind [11] [14] [46].
Die psychiatrische Neurochirurgie stellt gestörte neuronale Netzwerke und damit das Gehirn in den Mittelpunkt [2] [5]. Demgegenüber bezieht die *ME*-Hypothese — mit dem Fokus auf ein fehlgeleitetes Immunsystem und auf Entzündungen — den ganzen Körper mit ein und lässt traditionelle Neurotransmitter-Hypothesen in den Hintergrund treten [11] [13] [18].
Während die *ME*-Hypothese besonderes Augenmerk auf die Erforschung der Ursache psychischer Krankheiten legt, wird bei psychiatrischer Neurochirurgie bislang weniger

Ursachenforschung betrieben. Hier werden aufgrund verschiedener Paradigmen unterschiedliche Zielstrukturen läsioniert bzw. durch elektrische Stimulation deaktiviert, wobei die exakte Pathologie neuronaler Strukturen noch dringend zu eruieren ist [2] [4] [6] [37] [40].
Die *ME*-Hypothese wird vorrangig Therapieoptionen für frühe Krankheitsphasen liefern können [13] [14], wohingegen neurochirurgische Interventionen insbesondere bei chronisch und Therapie-refraktären Fällen einzusetzen sind [2] [5] [6].

8.2. Vergleich der ethischen Aspekte

In beiden Gruppen ((A) psychiatrische Neurochirurgie, (B) *ME*-Hypothese) wird auf das *Autonomieprinzip* eingegangen: Im Falle der psychiatrischen Neurochirurgie wird speziell die Herausforderung des *informierten Einverständnisses* betont [20] [23]. Im Falle der *ME*-Hypothese liegt der Schwerpunkt auf der *positiven Verpflichtung*, die Autonomie der PatientInnen wiederherzustellen [23].
In beiden Gruppen werden die *Prinzipien der Fürsorge* und des *Nicht-Schadens* im Rahmen einer *Nutzen-Risiko Analyse* dargestellt. Dabei hat unsere Analyse ergeben, dass die Effektivität und die Risiken der neuen Therapiemethoden (noch) nicht klar zu beurteilen sind. Gründe hierfür sind kleine Patientenzahlen, eine selektive Publikation von Ergebnissen und die ICD-10/DSM-5-basierte Auswahl von PatientInnen [2] [6] [36] [44].
Beide Gruppen verdeutlichen ein strukturelles Problem der psychiatrischen Forschung: Diagnosen stützen sich auf deskriptive Klassifikationssysteme, während die biomedizinische Ursache oft unbekannt ist [43] [44]. Invasive, risikoreiche Methoden wie *THS* sollten jedoch auf verifizierbaren Daten bezüglich ursächlicher Mechanismen beruhen [4] [6] [37] [40]. Biologische Untergruppen von Schizophrenie sollten identifiziert werden, um Medikamente zu entwickeln, die am Ursprung der Erkrankung ansetzen [13] [45].
Der Fokus der ethischen Diskussion psychiatrischer Neurochirurgie (*Publikation 2*) liegt auf dem Individuum und insbesondere dem Einsatz der Verfahren bei Minderjährigen [6] [38] [39].
Die ethische Diskussion der *ME*-Hypothese betrachtet darüber hinaus einen größeren gesellschaftlichen Kontext unter Einschluss von Rechtsprechung sowie möglichen Folgen für pharmazeutische Unternehmen und für die Stigmatisierung von PatientInnen.

Besonderes Augenmerk wird auf die beschränkten diagnostischen und therapeutischen Möglichkeiten in der Psychiatrie gelegt [44].
Die untersuchten Beispiele unterscheiden sich deutlich bezüglich der ethischen Evaluation und Legitimation von Zwangsbehandlungen: Neurochirurgische Zwangsbehandlungen der *AN* sind bei Minderjährigen und Erwachsenen unter keinen Umständen ethisch und rechtlich vertretbar [6] [39]. Demgegenüber ist die Zwangsmedikation mit entzündungshemmenden Medikamenten bei Schizophrenie ethisch weniger bedenklich. Sollte sich in weiteren Studien herausstellen, dass diese Medikamente an der Ursache der Erkrankung ansetzen, sind sie unter Umständen ethisch gerechtfertigt [23].

8.3. Limitationen

Limitationen finden sich methodisch bei der Anwendung der *Prinzipienethik von Beauchamp und Childress* [20]. Die Prinzipien können helfen, ethische Fragestellungen und Konflikte zu konkretisieren. Häufig helfen sie aber nicht, eine definitive Lösung zu finden [21].
Sowohl Eingriffe in das Gehirn, als auch Erkrankungen des Gehirnes können Persönlichkeitsveränderungen hervorrufen [6] [25]. Dieses wichtige ethische Problem kann mit Hilfe der *Prinzipienethik von Beauchamp und Childress* nicht adressiert werden. Die von Müller und Walter vertretene positive Verpflichtung, ggf. durch geeignete medizinische Maßnahmen die Autonomiefähigkeit von PatientInnen wiederherzustellen, geht über das von Beauchamp und Childress vertretene Verständnis des *Respekts vor der Autonomie* deutlich hinaus [22] [23] [25].
In *Publikation 2* konnten wir nur deutsch- und englischsprachige Artikel einbeziehen. Der asiatische Sprachraum wurde nicht erfasst, jedoch befindet sich dort ein großer Markt für neurochirurgische Eingriffe [3]. Außerdem wird geschätzt, dass nur ein kleiner Teil der neurochirurgisch behandelten Fälle insgesamt veröffentlicht wird [2] [4] [35] [36].
Die *Publikationen 3* und *4* diskutieren mit der *ME*-Hypothese eine medizinische Entwicklung, welche bislang noch nicht abgeschlossen ist. Es sind die ersten Beiträge in der Fachliteratur, welche sich mit ethischen Fragen und Folgen rund um die *ME*-Hypothese beschäftigen.

8.4. Ausblick und Kommentare anderer Autoren

Ein Übersichtsartikel zu den ethischen Herausforderungen der psychiatrischen Neurochirurgie, verfasst von Sabine Müller, ist in einem 2017 erschienenen Buch von Judy Illes zu finden [8].

Publikation 2 erhielt positive Kommentare von Autoren des Forschungsfeldes bezüglich der Aktualität des Themas und der umfangreichen Diskussion des *informierten Einverständnisses* [35] [50]. Entgegen unseren Empfehlungen plädieren die Autoren jedoch dafür, schon in frühen Krankheitsphasen neurochirurgisch einzugreifen, sowie Jugendliche in Studien einzuschließen, um langfristige kognitive Einschränkungen, regelmäßige Rückfälle und häufige Zwangsbehandlungen zu verhindern; zudem könne ein Eingriff in stabileren Krankheitsphasen die perioperative Morbidität und Mortalität reduzieren, sowie eine Entscheidung aus bloßer Verzweiflung verhindern [50] [51]. Barnett und Kollegen warnen vor einem Gehirn-orientierten Ansatz in der Therapie psychischer Erkrankungen; dieser Ansatz fördere bei PatientInnen das Gefühl, sie selbst könnten nichts gegen ihre Erkrankung tun [52].

Ein 2017 erschienener Artikel skizziert einen Leitfaden speziell für *THS* bei Patientinnen mit *AN* [4]; die Autoren betonen, ethische Belange — jenseits von Richtlinien der Ethikkomitees — ins Zentrum der *THS*-Forschung zu stellen [4]. Neben einer *Nutzen-Risiko-Analyse* und einem *informierten Einverständnis* wird die Versorgung der TeilnehmerInnen nach Ende des Forschungsprojektes, die Mitarbeit unabhängiger Ethiker, sowie der gleichberechtigte Zugang zu den (medizinischen) Produkten, welche aus dieser Forschung entstehen, thematisiert [4].

Die Entdeckung eines entzündlichen Geschehens bei Schizophrenie wird von Autoren des Forschungsfeldes als *„one of the hottest areas in schizophrenia research“* beschrieben [10]. Massenmedien wie die „Neue Zürcher Zeitung“ [53] greifen die Thematik bereits auf und machen sie der Allgemeinbevölkerung zugänglich.

Biologische Erklärungen psychischer Erkrankungen können, je nach Erkrankung und je nach Erklärungsmodell, stigmatisierend oder entstigmatisierend wirken [49] [54]. In vergangenen Studien wurden oft einzelne ätiologische Kategorien zusammengefasst (z.B. „bio-genetisch“), was die Effekte der einzelnen Komponenten verschleiert [54]. Eine neue Studie untersucht die Erklärungsmodelle im Einzelnen (z.B. „Genetik“, „chemisches Ungleichgewicht“, „belastende Lebensereignisse“) [54]. Bio-genetische Erklärungen können bei Alkoholabhängigkeit zur Entstigmatisierung beitragen [49] [54]. Bei

Schizophrenie ist jedoch nicht das Erklärungsmodell sondern die gefühlte Bedrohung und Instabilität, welche mit der Erkrankung einhergehen, der ausschlaggebende Aspekt für die Stigmatisierung [47] [54]. Demnach werden erfolgreiche Therapien am ehesten eine Entstigmatisierung bewirken [47].

8.5. Fazit

Ein biologisches Verständnis psychischer Erkrankungen kann Ausgangspunkt für die Entwicklung neuer Therapiemethoden sein. Forschung auf diesem Gebiet ist aufgrund der hohen Mortalität, einem meist chronischen Krankheitsverlauf und den schwerwiegenden Folgen für die geistige und körperliche Gesundheit ethisch gerechtfertigt. An den dargestellten Beispielen wird deutlich, dass innovative, biologisch orientierte Therapiemethoden früh in den Krankheitsprozess eingreifen, und somit die Folgen und das Vollbild der Erkrankung verhindern könnten (*ME*-Schizophrenie und entzündungshemmende Medikamente). Außerdem könnten sie die letzte Option für Therapie-refraktäre Fälle darstellen (Neurochirurgie). Dabei müssen der *Respekt vor der Patientenautonomie* und eine individuelle *Nutzen-Risiko-Analyse* immer Bestandteil eines diagnostischen und therapeutischen Vorgehens sein. Je invasiver der Eingriff, desto kritischer sollten diese Prinzipien geprüft werden. Hierfür ist eine lückenlose Veröffentlichung klinischer Studien und Einzelfallberichte unerlässlich. Zuletzt trägt die Biologisierung psychischer Erkrankungen dazu bei, die Psychiatrie und die somatische Medizin näher aneinander heranzuführen und damit einen ganzheitlichen Ansatz menschlicher Gesundheit zu verfolgen.

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10. Eidesstattliche Versicherung und Anteilserklärung

Eidesstattliche Versicherung

„Ich, Rita Riedmüller, versichere an Eides statt durch meine eigenhändige Unterschrift, dass ich die vorgelegte Dissertation mit dem Thema „Medizinethische Untersuchung innovativer Therapien für schwere psychiatrische Erkrankungen“ selbstständig und ohne nicht offengelegte Hilfe Dritter verfasst und keine anderen als die angegebenen Quellen und Hilfsmittel genutzt habe.
Alle Stellen, die wörtlich oder dem Sinne nach auf Publikationen oder Vorträgen anderer Autoren beruhen, sind als solche in korrekter Zitierung (siehe „Uniform Requirements for Manuscripts (URM)“ des ICMJE -*www.**icmje**.org*) kenntlich gemacht. Die Abschnitte zu Methodik (insbesondere praktische Arbeiten, Laborbestimmungen, statistische Aufarbeitung) und Resultaten (insbesondere Abbildungen, Graphiken und Tabellen) entsprechen den URM (s.o) und werden von mir verantwortet.
Meine Anteile an den ausgewählten Publikationen entsprechen denen, die in der untenstehenden gemeinsamen Erklärung mit der Betreuerin, angegeben sind. Sämtliche Publikationen, die aus dieser Dissertation hervorgegangen sind und bei denen ich Autorin bin, entsprechen den URM (s.o) und werden von mir verantwortet.
Die Bedeutung dieser eidesstattlichen Versicherung und die strafrechtlichen Folgen einer unwahren eidesstattlichen Versicherung (§156,161 des Strafgesetzbuches) sind mir bekannt und bewusst.“

Datum _____ Unterschrift

Anteilserklärung an den erfolgten Publikationen

Rita Riedmüller hatte folgenden Anteil an den folgenden Publikationen:

Publikation 1:

Müller, **Riedmüller**, Van Oosterhout: „Rivaling paradigms in psychiatric neurosurgery: adjustability versus quick fix versus minimal-invasiveness“, Frontiers in Integrative Neuroscience, 2015.
Beitrag im Einzelnen:
- Mitarbeit an der Literaturrecherche (30%)
- Mitarbeit an der Verfassung des Textes: Rita Riedmüller hat die Absätze zu Anorexia nervosa geschrieben, und die Abschnitte „Efficacy - Deep Brain Stimulation“ sowie „Adverse Effects - Deep Brain Stimulation“ (vgl. Seite 2 unten bis Seite 3 des Papers)

Publikation 2:

Müller, **Riedmüller**, Walter, Christen: „Ethical Evaluation of Stereotactic Neurosurgery for Anorexia Nervosa“, American Journal of Bioethics Section Neuroscience, 2015.
Beitrag im Einzelnen:
- Erste Recherche relevanter Primär- und Sekundär-Literatur, welche zu einem späteren Zeitpunkt wiederholt und vervollständigt wurde
- Substantielle Mitarbeit an der Konzeption des gesamten Papers
- Mitarbeit an der Verfassung des Textes: Abschnitt „Anorexia nervosa - Definition, Prevalence, Comorbidity“ und „Anorexia nervosa - Neuronal Correlates“.
- Mitarbeit an den Tabellen: Tabelle 1 (100%)
- Aus dem Abschnitt „Ethical discussion“ hat Rita Riedmüller folgende Abschnitte geschrieben: „Doubtable Therapy-Resistance“ und „Coercive Interventions in the Brains of Adolescents“
- Mitarbeit an der Revision des Papers

Publikation 3:

Riedmüller and Müller: „Ethical Implications of the Mild Encephalitis Hypothesis of Schizophrenia“, Frontiers in Psychiatry Section Schizophrenia, 2017.
Beitrag im Einzelnen:
- Maßgeblicher Beitrag zur Konzeption des Papers (80%)
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- Hauptanteil an der Revision des Manuskriptes (80%)
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Publikation 4:

Müller and **Riedmüller**: „How will the Mild Encephalitis Hypothesis of Schizophrenia influence stigmatization?“, Frontiers in Psychiatry Section Schizophrenia, 2017.
Beitrag im Einzelnen:

- Mitarbeit an der Konzeption (50%)
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- Mitarbeit an der Verfassung des Manuskriptes (30%)
- Überarbeitung nach Review Prozess (50%)

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11. Druckexemplare der ausgewählten Publikationen

11.1. Müller, Riedmüller, Van Oosterhout: „Rivaling paradigms in psychiatric neurosurgery: adjustability versus quick fix versus minimal-invasiveness“, Frontiers in Integrative Neuroscience, 2015. 9:27. DOI: 10.3389/fnint.2015.00027.

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Rivaling paradigms in psychiatric neurosurgery: adjustability versus quick fix versus minimal-invasiveness

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In the wake of deep brain stimulation (DBS) development, ablative neurosurgical procedures are seeing a comeback, although they had been discredited and nearly completely abandoned in the 1970s because of their unethical practice. Modern stereotactic ablative procedures as thermal or radiofrequency ablation, and particularly radiosurgery (e.g., Gamma Knife) are much safer than the historical procedures, so that a re-evaluation of this technique is required. The different approaches of modern psychiatric neurosurgery refer to different paradigms: microsurgical ablative procedures is based on the paradigm 'quick fix,' radiosurgery on the paradigm 'minimal-invasiveness,' and DBS on the paradigm 'adjustability.' From a mere medical perspective, none of the procedures is absolutely superior; rather, they have different profiles of advantages and disadvantages. Therefore, individual factors are crucial in decision-making, particularly the patients' social situation, individual preferences, and individual attitudes. The different approaches are not only rivals, but also enriching mutually. DBS is preferable for exploring new targets, which may become candidates for ablative microsurgery or radiosurgery.

Keywords: psychiatric neurosurgery, radiosurgery, gamma knife, DBS, ablative neurosurgery, cingulotomy, capsulotomy, neuroethics

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Introduction

Since 2000, there is a renaissance of neurosurgical treatments of psychiatric disorders. Many researchers and clinicians hope that modern neurosurgical approaches will be established as treatment options for a growing number of therapy-refractory psychiatric disorders. About 90% of functional neurosurgeons feel optimistic about the future of psychiatric neurosurgery (Lipsman et al., 2011; Mendelsohn et al., 2013).

Modern psychiatric neurosurgery includes DBS and ablative neurosurgical procedures (thermal or radiofrequency ablation, and radiosurgery). DBS and thermal or radiofrequency ablation procedures require a craniotomy. Radiosurgery (Gamma Knife Radiosurgery) is performed without craniotomy, mostly as an ambulant treatment. In future, high intensity focused ultrasound might

Abbreviations: ALIC, anterior limb of the internal capsule; DBS, deep brain stimulation; ITP, inferior thalamic peduncule; MRI, magnetic resonance imaging; NAcc, nucleus accumbens; OCD, obsessive-compulsive disorder; SCC, subgenual cingulate cortex; slMFB, superolateral medial forebrain bundle; VC/VS, ventral capsula/ventral striatum.

become another option. The worldwide first four patients have been treated with this technique in South Korea (Na et al., 2015).

Many authors consider DBS as the most modern and superior technology, particularly because of its adjustability and high degree of reversibility. However, in the wake of DBS development, ablative neurosurgical procedures are seeing a comeback, although they had been discredited and nearly completely abandoned in the 1970s because of their frequent serious complications and their unethical practice. Since modern stereotactic ablative procedures, particularly radiosurgery are much safer and more efficient than their historical antecessors, a re-evaluation of this technique is required.

Until now, ethical discussion about non-DBS psychiatric neurosurgery is scarce, whereas psychiatric DBS is intensively discussed ethically. This blind spot in neuroethics is astonishing for several reasons: First, the fraction of ablative procedures in psychiatric neurosurgery is big: in North America, 50% of psychiatric neurosurgeons use lesioning exclusively or combined with DBS (Lipsman et al., 2011); outside of North America even 54.9% (Mendelsohn et al., 2013). Second, two expert panels have affirmed stereotactic ablative procedures as important alternatives for appropriately selected patients (Parkinsonism: Bronstein et al., 2011; psychiatric disorders: Nuttin et al., 2014). Third, a clear superiority of any procedure in all relevant aspects cannot be established. Forth, which approach is optimal, depends significantly on patients' individual medical and non-medical properties. Fifth, the much higher costs of DBS, particularly for long-term treatment, exclude this option for the majority of patients world-wide.

Therefore, a comprehensive ethical analysis of the pros and cons of the different approaches is necessary, based on clinical facts, not on ideological prejudices. Particularly, it is not justified to characterize modern lesioning procedures as successors of historical psychosurgery, while presenting DBS as something quite different. In fact, both psychiatric DBS and modern ablative psychiatric neurosurgery are significantly improved successors of the historical psychosurgery.

Different Paradigms

The different approaches of modern psychiatric neurosurgery refer to different paradigms: microsurgical ablative procedures is based on the paradigm 'quick fix,' radiosurgery on the paradigm 'minimal-invasiveness,' and DBS on the paradigm 'adjustability.'

The purpose of ablative microsurgical procedures is to disconnect limbic system circuits related to different psychiatric disorders in order to enhance brain function and reduce psychiatric symptoms (Martinez-Alvarez, 2015).

Radiosurgery is usually considered as an ablative treatment. However, recent neurophysiological, radiological, and histological studies challenge this view. Radiosurgical protocols for neurological or psychiatric disorders might have differential effects on various neuronal populations and remodel the glial environment, leading to a modulation of function while preserving basic processing. Thus, modern functional radiosurgery might be based on neuromodulatory effects (Régis, 2013).

DBS has been considered as a method to produce reversible lesions. Indeed, high-frequency DBS has a similar effect as lesions, i.e., inhibition of targets that are hyperactive in psychiatric disorders. However, its mechanism of action is unclear, and several hypotheses have been put forward to explain the blocking effect of stimulation (Lévèque, 2014). Its main advantage is that the stimulation effect can be adjusted by adapting the stimulation parameters.

Efficacy

A direct comparison of the efficacy of the different approaches is not yet possible, particularly because of the heterogeneity of the studies, the small patient numbers, and the fact that most studies are neither placebo-controlled nor double-blind. The rapid development of the methods aggravates their comparison: In psychiatric DBS, many targets (mostly overlapping for different diagnoses) are tested with different stimulation parameters. In radiosurgery, the radiation doses used decreased significantly. Randomized controlled trials would be optimal to directly compare the efficacy of the different approaches. However, this scientific standard cannot be met for practical and ethical reasons. Nevertheless, studies that directly compare different approaches with matched patients would also provide a valid efficacy comparison. In any case, this would be much better than the current practice of publishing reviews. The problem with most reviews is that they summarize only data published in medical journals in English language. However, this practice does not represent the clinical reality but presents a distorted picture. Therefore, we expect a severe publication bias (Schläpfer and Fins, 2010), leading to a systematic over-evaluation of the benefits.

The publication bias is no minor problem in psychiatric neurosurgery, but a fundamental problem, which corrupts the evaluation of risks and benefits of the different procedures. For example, we have performed a systematic literature search on psychiatric neurosurgery for treating anorexia nervosa, which yielded only 27 cases (Müller et al., forthcoming). However, from presentations on conferences we learned that a multiple of the patients reported in journals have been treated with ablative neurosurgery. Websites of private clinics in Europe as well as in Asia offer ablative surgery for a broad spectrum of psychiatric disorders as part of clinical routine. These treatments are not part of clinical studies and usually not published. Recently, a book of Sun and De Salles (2015) has been published which presents original data from several studies with ablative neurosurgery for different psychiatric disorders which had not been published in medical journals.

That being said, we summarize available data on the efficacy of the different approaches, whereby we refer to the most recent reviews as well as to the above mentioned book of Sun and De Salles.

Deep Brain Stimulation

For OCD, data from 25 papers comprising 109 patients and five targets (NAcc, VC/VS, ITP, nucleus subthalamicus, and internal

capsule) have been published (Kohl et al., 2014). The responder rates ranged from 45.5 to 100%.

For depression, data from 22 papers comprising 188 patients and six targets (NAcc, VC/VS, SCC, lateral habenula, ITP, and slMFB) have been published (Morishita et al., 2014). The responder rates ranged from 29 to 92%. However, two multicenter, randomized, controlled, prospective studies evaluating the efficacy of VC/VS, and SCC DBS were recently discontinued because of inefficacy based on futility analyses (Morishita et al., 2014). The failure of two high quality studies in spite of the universally positive results of reported open-label trials could be attributable to the typical overestimation of efficacy associated with open label trials that arises from the failure to control for placebo, and biases due to lack of blinding and randomization (Morishita et al., 2014).

For anorexia nervosa, six papers comprising 18 patients and three targets (NAcc, subcallosal cingulum, and VC/VS) have been published (Müller et al., forthcoming). Remission (normalized body mass index) occurred in 61% of patients, and in 88.9%, psychiatric comorbidities improved, too. However, Sun et al. (2015) have recently published less favorable results: only 20% (3/15) of their patients treated with NAcc DBS showed improvements in symptoms. The other 80% underwent a second surgery (anterior capsulotomy), which improved eating behavior and psychiatric symptoms in all patients (Sun et al., 2015).

Generally, the current knowledge does not allow for identifying a superior target (Kohl et al., 2014; Morishita et al., 2014; Müller et al., forthcoming).

Microsurgical Ablative Procedures

For treatment-refractory depression, 40–60% of patients responded to bilateral capsulotomy or cingulotomy performed with thermal coagulation or radiosurgery (Eljamel, 2015).

For OCD, response rates between 36 and 89% have been published (Martinez-Alvarez, 2015). Martinez-Alvarez (2015) reports own data of 100 OCD patients of whom 71% responded.

For anorexia nervosa, three papers with nine patients report a remission rate of 100%, with regard to both weight normalization and psychiatric comorbidities. Different targets were used (dorsomedial thalamus, anterior capsula, NAcc; Müller et al., forthcoming). Sun et al. (2015) report 150 patients treated with capsulotomy, of whom 85% experienced an improvement in symptoms.

Radiosurgical Ablative Procedures

For OCD patients, a response rate of 70% has been reported in the literature (Martinez-Alvarez, 2015). Martinez-Alvarez (2015) reported a response rate of 100% in five own patients.

Adverse Effects

Deep Brain Stimulation

Following DBS, surgery-related, device-related, and stimulation-related side-effects have been reported. Serious adverse events during surgery were reported: seizures, intracerebral hemorrhages (in one case causing a temporary hemiparesis), a panic attack, and a cardiac air embolus (Kohl et al., 2014; Morishita et al., 2014; Müller et al., forthcoming). In anorexia nervosa patients, a high rate of severe complications have been reported: further weight loss, pancreatitis, hypophosphataemia, hypokalaemia, a refeeding delirium, an epileptic seizure during electrode programming, QT prolongation, and worsening of mood (Müller et al., forthcoming).

In several cases, superficial wound infections, inflammation, or allergic reactions occurred (Kohl et al., 2014). Device-related adverse effects comprised breaks in stimulating leads or extension wires requiring replacement, dysesthesia in the subclavicular region, and feelings of the leads or stimulators (Kohl et al., 2014).

Stimulation-induced adverse effects comprised mood disturbances, suicidality, anxiety, panic attacks, fatigue, and hypomania, partly induced either by a change of stimulation parameters, or by battery depletion. These effects were either adjustable by parameter adaption or device exchange (Kohl et al., 2014; Morishita et al., 2014; Müller et al., forthcoming). Some DBS patients report feelings of self-estrangement (Gilbert, 2013). A great problem is the high number of suicides and suicide attempts after DBS that have been reported in eight papers (Kohl et al., 2014; Morishita et al., 2014). Further side effects include vertigo, weight loss or gain, long-lasting fatigue, an increased headache frequency, and visual disturbance (Kohl et al., 2014).

Microsurgical Ablative Procedures

Adverse side effects of microsurgical ablative surgery for major depression comprised epilepsy (up to 10%), incontinence, weight gain, transient confusion, transient mania, and transient incontinence. Further side effects reported by only one or two studies are personality change (7 and 10%), lethargy, hemiplegia (0.3%), and suicide (1 and 9%) (Eljamel, 2015). Following microsurgical ablative surgery for treating OCD, a similar spectrum of adverse effects has been published. Most side effects were transient, and included headaches, urinary incontinence, impaired cognitive function, and confusion. Tardive epileptic seizures occurred in 2–9% of patients (Martinez-Alvarez, 2015). In case of anorexia nervosa, the journal papers reported only transient adverse effects: bradycardia, mild disorientation, moderate somnolence, loss of concentration, apathy, emotional emptiness and mild loss of decorum, headaches, and centric fever (Müller et al., forthcoming). However, Sun et al. (2015) report intracranial hematomas in 1.9% of the patients (4/216); one patient died thereof (0.5%).

Radiosurgical Ablative Procedures

Side-effects such as fatigue, weight gain, or apathy occurred in several patients who had received doses of more than 180 Gy. In newer studies with lower radiation doses, adverse effects did not occur (Lévèque, 2014).

Recommendations

From a mere medical perspective, none of the procedures is absolutely superior; rather, they have different profiles of advantages and disadvantages (see **Table 1**). The main advantages of DBS are

TABLE 1 | Comparison of different approaches of modern psychiatric neurosurgery.

	DBS	Microsurgery	Radiosurgery
Paradigm	Adjustability	Quick fix	Minimal-invasiveness
Adjustability	Very high	Low (through a second intervention to produce another lesion or to enlarge the lesion)	Low (second intervention to produce another lesion) to medium (through a step-by-step approach)
Addressing different targets in a single session	No	Yes	Yes
Reversibility	High (exception: permanent adverse effects due to lesions, infections, bleeding)	No	No
Invasive craniotomy	Yes	Yes	No
Onset of action	Hours to 12 months	Days or weeks	6–12 months
Appropriateness for patients with special needs	No	Patients who would not comply with long-term follow-up	Patients - Who would not comply with long-term follow-up - With higher risks of anesthesia - With higher infection risks
Time and effort of the procedure	Single surgery; several days in hospital plus visits for adapting stimulation parameters	Single surgery; several days in hospital	Ambulatory treatment, single session
Long-term treatment	Frequent consultation of specialists required (parameter adjustment, device exchange)	Not necessary	Not necessary
Costs	Very high direct and life-long costs	Medium	Low
Mortality risk	Yes	Yes	No
Short-term risks	- Anesthesia - Infection - Hemorrhage - Hardware complications	- Anesthesia - Infection - Hemorrhage	- Development of cysts - Edemas
Long-term risks	- Infection risks (due to biofilms and regular battery exchange) - Hardware complications	No	No
Possible adverse effects	- Suicidality - Mood disturbance - Anxiety - Panic attacks - Hypomania - Weight loss or gain - Long-lasting fatigue - Increased headache frequency - Visual disturbance	- Suicidality - Headaches - Seizures - Drowsiness - Urinary incontinence Cognitive impairment - Personality change	- Transient cognitive impairment - Transient apathy - Radiation dose >180 Gy: fatigue, weight gain, or apathy
Disadvantages in daily life	Device-related problems in daily life (e.g., at airport controls)	No	No
Disadvantages for further medical treatment	- Exclusion of electroconvulsive therapy - Special MRI required	No	No
Possible problems of psychosocial adaptation	Self-estrangement, feeling of being manipulated; burden of normality syndrome	Burden of normality syndrome	Improbable

its adaptability and high degree of reversibility; of microsurgical ablative procedures the rapid onset of action; and of radiosurgery its noninvasiveness and low rate of adverse effects. Furthermore, it differs individually what counts as an advantage or disadvantage: For example, the delayed onset of action of radiosurgery makes it disadvantageous for patients who need a rapid symptom reduction. However, the gradual development of effects might be advantageous since it alleviates the psychological adjustment (Lindquist et al., 1991). This may be protective against feelings of being manipulated, self-estrangement and the burden of normality syndrome.

We support further research in this area generally, but think that therapeutic adventurism cannot be justified. The current research practice in psychiatric neurosurgery does not fulfill the highest ethical and scientific standards. We plead for ethical reasons for better safeguards in research and clinical practice. Since psychiatric neurosurgery has both the goal and the potential to change core features of the patients' personalities, these interventions require a solid scientific fundament. Particularly, we recommend the following:

- Case registries should become obligatory for all clinical studies in order to avoid a publication bias and its negative consequences, namely faulty evaluations of therapies, flawed therapy recommendations, unpromising treatment attempts and unneeded clinical studies (Morishita et al., 2014). Individual treatment attempts should not be performed.

- A multi-center, randomized, controlled study should be performed that directly compares DBS, microsurgical ablative procedures and radiosurgery for different psychiatric disorders.
- Since multiple circuits seem to be involved in psychiatric disorders, targets of DBS or ablative procedures, respectively, should be selected specifically with regard to the prominent symptoms instead of using the institution-specific target for all patients.
- Since no single procedure is absolutely superior, patients should be informed comprehensively about the different treatment options and their respective benefit-risk-profiles. Individual factors have to be crucial in decision making, particularly the patients' social situation, individual preferences, and individual attitudes (e.g., whether they could tolerate implanted devices; whether they are more afraid of the irreversibility of an ablative procedure or of the medical risks of brain surgery).

We are convinced that the different approaches are not only rivals, but also enriching mutually. DBS is preferable for exploring new targets, which may become candidates for ablative microsurgery or radiosurgery.

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11.2. Müller, Riedmüller, Walter, Christen: „An Ethical Evaluation of Stereotactic Neurosur-gery for Anorexia Nervosa“, American Journal of Bioethics Neuroscience, 2015. 6:4, 50-65, DOI: 10.1080/21507740.2015.1094536.

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11.3. Riedmüller and Müller: „Ethical Implications of the Mild Encephalitis Hypothesis of Schizophrenia“, Frontiers in Psychiatry, 2017. 8:38. DOI: 10.3389/fpsyt.2017.00038.

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Ethical Implications of the Mild Encephalitis Hypothesis of Schizophrenia

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Schizophrenia is a serious mental disease with a high mortality rate and severe social consequences. Due to insufficient knowledge about its etiopathogenesis, curative treatments are not available. One of the most promising new research concepts is the mild encephalitis hypothesis of schizophrenia, developed mainly by Karl Bechter and Norbert Müller. According to this hypothesis, a significant subgroup of schizophrenia patients suffer from a mild, but chronic, form of encephalitis with markedly different etiologies ranging from viral infections, traumas to autoimmune diseases. This inflammatory process is thought to occur in the beginning or during the course of the disease. In this article, we investigate the consequences of the mild encephalitis hypothesis of schizophrenia for the scientific community, and evaluate these consequences ethically. The mild encephalitis hypothesis implies that schizophrenia would no longer be considered an incurable psychiatric disorder. Instead, it would be considered a chronic, but treatable, neurological disease. This paradigm shift would doubtlessly have significant consequences: (1) major reforms would be necessary in the theoretical conceptualization of schizophrenia, which would challenge the psychiatric diagnostic systems, Diagnostic and Statistical Manual of Mental Disorders version 5 and ICD-10. (2) Psychotic patients should be treated in interdisciplinary teams, optimally in neuropsychiatric units; additionally, specialists for endocrinology, diabetology, and cardiology should be consulted for the frequently occuring somatic comorbidities. (3) Current diagnostic procedures and (4) therapies would have to be modified significantly. (5) There might be repercussions for the pharmaceutical industry as well: first, because old drugs with expired patent protection could partly replace expensive drugs and, second, because there would be a demand for the development of new anti-inflammatory drugs. (6) Legal evaluation of compulsory treatment orders might have to be reconsidered in light of causal therapies; leading to increased legal approval and reduced need for compulsory treatment orders due to better patient compliance. (7) The social inclusion of patients might improve, if treatment became more effective regarding cognitive and social functioning. (8) The stigmatization of patients and their relatives might decrease.

Keywords: schizophrenia, ethics, medical, mild encephalitis, stigmatization, compulsory treatment, autoimmune encephalitis

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Abbreviations: COX-2, cyclooxygenase-2; CSF, cerebrospinal fluid; CT, computer tomography; DSM-5, Diagnostic and Statistical Manual of Mental Disorders version 5; FDG-PET, fluorodeoxyglucose positron emission tomography; NAC, *N*-acetylcysteine; NMDA, *N*-methyl-D-aspartate; NMDAR, *N*-methyl-D-aspartate receptor; MRI, magnetic resonance imaging; PUFA, poly-unsaturated fatty acids; RDoC, Research Domain Criteria project.

INTRODUCTION

Schizophrenia is a severe psychiatric disease that affects about 1% of the worldwide population. It is characterized by hallucinations, delusions, disorganization of thought and behavior, depression, flattened affect, cognitive disorders, and social withdrawal. In most cases, the disease takes a chronic, relapsing-remitting course with progressive cognitive decline and a significantly reduced life-expectancy. Most patients are excluded from society because of their bizarre and sometimes frightening behavior, and—depending on the societal system—end up in special care homes, asylums or jails, on the street, or are even executed. Human Rights Watch (1) states that "US prisons and jails have taken on the role of mental health facilities" as a consequence of the "limited availability of community-based outpatients and residential mental health programs and resources." In the USA, direct and indirect costs of schizophrenia amounted to approximately 62.7 billion in 2002 (2). Between 1.5 and 3% of the total national health-care expenditures are spent on patients with schizophrenia (3).

The pathophysiology of schizophrenia is still unknown (4). Standard therapies against schizophrenia are only symptomatic and provide control rather than cure (5). Antipsychotics, the standard drugs, are criticized because of severe side effects, including metabolic syndrome and brain atrophy (6, 7). More and more evidence supports the hypothesis that schizophrenia is a neurological disease rather than a psychosocial disorder. One important piece of evidence is the recent discovery of anti-NMDA receptor encephalitis (8), which causes psychotic states leading, in some cases, to a misdiagnosis of schizophrenia (9).

One of the most promising new research concepts is the mild encephalitis hypothesis of schizophrenia, developed mainly by the German psychiatrists, Karl Bechter and Norbert Müller (10–15). According to this hypothesis, a significant subgroup of patients with schizophrenia suffer from a mild, but chronic form of encephalitis which can have quite different etiologies ranging from viral infections, traumas to autoimmune diseases. At least in a subgroup of schizophrenia patients, inflammatory processes occur in the beginning or during the course of the disease (16–20). Therefore, anti-inflammatory drugs might be effective. Indeed, several small, but high quality studies have shown significant effectiveness of several anti-inflammatory drugs such as aspirin and *N*-acetylcysteine as add-on medication to antipsychotic drugs, particularly for first-episode psychosis patients (18, 20, 21). Since different etiologies (genetically caused, immunological, growth factor-related, acquired, etc.) can underlie psychotic symptoms, a careful differential diagnosis is necessary. The aim of this article is not to provide a comprehensive review, but to focus on arising ethical questions.

The mild encephalitis hypothesis implies that schizophrenia would no longer be considered an incurable psychiatric disorder, but instead, a chronic, and in many cases, treatable neurological disease. With this paradigm shift, significant consequences could be expected for (1) the theoretical conceptualization of schizophrenia, which will challenge the psychiatric diagnostic systems, Diagnostic and Statistical Manual of Mental Disorders version 5 (DSM-5) and ICD-10; (2) the medical discipline in charge of schizophrenia patients; (3) the diagnostic procedures; (4) the therapies; (5) the pharmaceutical industry; (6) the legal evaluation of compulsory drug treatment; (7) the social inclusion of patients; and (8) the stigmatization of patients and their relatives.

We proceed with a general description of schizophrenia (part 2). Then, we present the mild encephalitis hypothesis of schizophrenia, discussing the available scientific evidence (part 3). Finally, we investigate which consequences could be expected of the mild encephalitis hypothesis of schizophrenia, and evaluate these consequences ethically (part 4).

SCHIZOPHRENIA

The recent psychiatric diagnostic systems ICD-10 and DSM-5 ground on a nominalistic concept of mental diseases, which is agnostic with regard to etiology and neuropathology.

Symptoms of schizophrenia are categorized into two classes: positive symptoms describe an excess of normal functions (e.g., delusions, hallucinations, disorganized speech, and behavior) and negative symptoms a decline or loss of normal functioning (diminished emotional expression or avolition).

The DSM-5 defines schizophrenia by six criteria (A–F) (22). Criterion A requires for the diagnosis of schizophrenia that at least two of five characteristic symptoms (1. delusions, 2. hallucinations, 3. disorganized speech, 4. grossly disorganized or catatonic behavior, and 5. negative symptoms) are present for a significant portion of time during a 1-month period (or less if successfully treated). Criterion B refers to social/occupational dysfunction, and Criterion C defines the required duration of symptoms. Criteria D–F distinguish schizophrenia from other disorders. Particularly, Criterion E excludes a diagnosis of schizophrenia if the disturbance is attributable to physiological effects of a substance or another medical condition.

Clinical Course

Psychotic features of schizophrenia typically appear between the late teens and mid-30s. Sustained recovery occurs in less than 30%; relapse rates are very high and reach approximately 80% (4). In the majority of patients, the illness becomes chronic with severe social consequences: in Europe, only 20% of people with schizophrenia are employed. In the USA, 20% are homeless 1 year after the diagnosis (4). Individuals with schizophrenia are at increased risk to become violent offenders (23). The risk of committing a violent offense is 4.6-fold increased in men, and even 23.2-fold in women (24).

People with schizophrenia have high comorbidity rates for further psychiatric disorders, particularly substance abuse, obsessive-compulsive disorder, and panic disorder (22).

Apart from psychotic symptoms, people with schizophrenia often suffer from inappropriate affect, disturbed sleeping patterns, lack of interest in eating, somatic concerns, impulsiveness, reduced attention, and deficits in Theory of Mind (22).

Furthermore, schizophrenia is associated with general medical risk factors: a higher prevalence of obesity, diabetes mellitus (partly due to atypical antipsychotics), and hypertension. These risk factors lead to an elevated risk for chronic illnesses, such as coronary heart disease, metabolic syndrome, and pulmonary diseases (22).

Patients with schizophrenia have twofold to threefold higher mortality rates compared to the general population. Life expectancy is reduced by 10–25 years (25). Four main reasons contribute to the higher mortality rate: comorbid physical illnesses, insufficient physical health care, adverse effects of antipsychotic medication, and suicides (25). Approximately 20% of patients with schizophrenia attempt suicide, while 5–6% die by suicide (22).

Genetic and Environmental Factors

The heritability of schizophrenia is about 80%, but the search for its genetic basis has been frustrating (26). Schizophrenia is a polygenetic disorder. A genome-wide association study discovered 108 schizophrenia-associated genetic loci, many of which are involved in important immune functions, particularly in acquired immunity (27). This finding is conceptually in line with the mild encephalitis hypothesis (13).

The vulnerability-stress model has been the prominent explanatory model for schizophrenia during the past decades (15). Neither the genetic code nor the environment is the sole cause for schizophrenia. Rather the effect of an individual's genotype depends on environmental exposure and, *vice versa*, the effect of environmental exposure on risk depends on an individual's genotype (13, 26). The incidence of schizophrenia is twofold to fourfold increased in people living in or raised in urban areas, in migrant and minority ethnic groups, in cannabis users, and in people with childhood adversity (26).

Neurotransmitter Disturbances and Reduced Brain Volume

Disturbances in neurotransmitters and receptors have been postulated for decades in diverse hypotheses of schizophrenia, especially imbalances in dopamine, glutamate, and serotonin systems. It is assumed that hypofunction of dopaminergic projections from mesolimbic to prefrontal structures causes negative symptoms and that a subcortical excess of dopamine is responsible for positive symptoms (28). The main source of serotonin, the dorsal raphe nucleus, is hypothesized to be chronically upregulated due to stress in schizophrenic patients; this can influence glutamatergic transmission and inhibit dopaminergic neurons, thus causing negative symptoms (29).

Magnetic resonance imaging (MRI) studies demonstrated a progressive loss of brain volume in patients with schizophrenia. Both gray and white matter damage is already present in prodromal and first-episode psychosis patients (6, 7). The reduction of gray matter is associated with elevated peripheral inflammatory markers (7). However, findings of MRI studies are valid on a group level, and do not allow individual diagnoses.

Treatment

First-generation antipsychotic agents (FGA, typical antipsychotics), such as haloperidol, fluphenazine, and chlorpromazine, exert their effects by blocking dopamine receptors and thus decreasing mainly positive symptoms (30). However, FGAs have severe side effects, e.g., deterioration of negative symptoms and cognition, prolactin elevation, acute and chronic movement disorders, such as tremor, rigidity, and tardive dyskinesia (30).

Second-generation antipsychotic agents (SGA, atypical antipsychotics), e.g., clozapine, olanzapine, and quetiapine also block dopamine receptors, but additionally influence serotonin and norepinephrine receptors, which makes them more effective against negative symptoms (28, 30). While SGA do not evoke the typical FGA side effects, they have other severe adverse effects such as agranulocytosis (reduction of white blood cells), weight gain, and alterations in glucose and lipid metabolism (30).

Although brain volume of schizophrenic patients is already reduced before the beginning of antipsychotic medication, both FGAs and SGAs seem to increase this effect (6, 7). The cumulative antipsychotic medication can cause neurocognitive decline, negative and positive symptoms, and worsen psychosocial functioning (6). Cognitive deficits and negative symptoms respond only modestly to antipsychotic medication (4). Neither FGAs nor SGAs improve functional recovery (e.g., employment) (4).

Anti-epileptic agents can be added for reducing aggression and impulsiveness, and antidepressants to reduce depression, anxiety, and if necessary craving for drugs.

Psycho-educational and coping-oriented interventions, cognitive behavioral therapy, cognitive remediation, social skills training, and assertive community treatment can help patients to reintegrate and participate in the community (30). Supportive therapies for family members and patients can enhance medication adherence and help to cope with persistent psychotic symptoms (30).

THE MILD ENCEPHALITIS HYPOTHESIS OF SCHIZOPHRENIA

The hypothesis that infections could play a part in the development of schizophrenia is not new: the association between bacterial infections and psychosis was already proposed in 1896 (31). Later on, psychosis and schizophrenic symptoms were hypothesized as consequences of the influenza pandemia in 1918. Unfortunately, these theories were not further investigated due to a lack of relevant treatment methods and the growing prominence of Freudian theories (31). Today, the role of inflammation in psychiatric disorders has become one of the most promising research fields (21).

The mild encephalitis hypothesis published by Karl Bechter in 2001 and updated in the following years, explains the pathophysiology of a subgroup of severe psychiatric disorders, especially of schizophrenic and affective psychoses, in terms of a mild encephalitis. This hypothesis is based on findings from immunology, cerebrospinal fluid (CSF) investigations, imaging studies, and clinical observations. Mild encephalitis is a non-lethal, low grade cellular-infiltrative and/or humoral brain inflammation, possibly accompanied by neurological soft but not hard signs (12). The demarcation between "classical" encephalitis and "mild" encephalitis is important, since "mild" points to the so-called "low-level neuroinflammation" (12). This term is used in clinical publications to describe molecular or cellular abnormalities of minor degree (12).

According to the mild encephalitis hypothesis, the reduced brain volume of schizophrenia patients could be a consequence of mild inflammatory states, which are caused by trauma or various types of toxicity (12). Indeed, elevated cytokine levels are correlated with brain volume loss (7, 12, 14). Inflammation can also disturb brain development of unborn children: during the second half of pregnancy, maternal levels of serum IL-8 (sensitive inflammatory marker) are associated with decreased cortical volumes and an elevated risk for schizophrenia in the offspring (14).

A multitude of factors can trigger mild inflammation, e.g., infections, autoimmunity, toxicity, and trauma; this is modulated by genetic and environmental factors, and immune status (12).

Several lines of evidence support the mild encephalitis hypothesis of schizophrenia.

1. Patients with schizophrenia have increased levels of certain inflammatory markers.
2. Inflammatory processes in the brain can disturb neurotransmitter metabolism.
3. Infections, both prenatal and postnatal, can increase the risk of schizophrenia.
4. There is a correlation between autoimmune diseases and schizophrenia which could be linked to inflammatory events.

Inflammatory Processes

According to the vulnerability-stress model of schizophrenia, physical and mental stress can cause psychotic episodes. Inflammation could be the missing link between stress and psychosis (15). Stress deteriorates the body's ability to fight infections, triggers autoimmune activity (32), and increases the production of pro-inflammatory cytokines (15, 16, 31, 33). Pro-inflammatory cytokines are key regulators of inflammation, whereas anti-inflammatory cytokines can inhibit the production of their pro-inflammatory counterparts. Cytokines can affect neurotransmitter levels and microglial activation (33). Microglial cells fight invading antigens, influence growth and apoptosis of neural cells, and can produce cytokines (19). Microglia can be "primed" so that they respond even to a small, second stimulus (14, 15). Thus, cytokine production by microglia can become chronic and also proceed in the absence of the initial trigger.

Schizophrenic patients seem to be in such a heightened inflammatory state: in non-medicated schizophrenic patients, cytokine levels are increased (15, 19). Activated microglia have been detected in patients with recent-onset schizophrenia (15).

Infections

Maternal immune activation is an important risk factor for schizophrenia and autism in the offspring (15, 34). Inflammation during pregnancy could alter normal neurodevelopment, gene expression, and immune function in the unborn child (34–36). Epidemiological studies, prospective birth studies, and animal studies support the hypothesis that maternal immune activation can cause life-long neuropathology and altered behavior in the offspring. Most maternal infections act as a disease primer ("first hit") making the individual more susceptible to the effects of genetic mutations and environmental exposures (20, 34).

CNS infections in childhood and in adulthood also elevate the risk of schizophrenia (20, 31). Likely, in both prenatal and postnatal infections, the schizophrenia risk is rather elevated by the immune response (inflammatory cytokines, antibodies), instead of a specific pathogen being responsible for the disease (15, 31, 34–36). As a matter of fact, the risk of developing schizophrenia is associated with the number of severe infections, following a dose–response relationship (31).

Nevertheless, infections with the parasite *Toxoplasma gondii* play a special part in schizophrenia. According to a recent meta-analysis, the evidence for an association between schizophrenia and *T. gondii* is "overwhelming" (37): the prevalence of *T. gondii* antibodies is 1.43-fold higher than in controls (37). A similar association exists for obsessive–compulsive disorder, bipolar disorder, and possibly addiction (37). Presumably, a latent infection with *T. gondii* is reactivated in patients with schizophrenia. The underlying mechanism might be *T. gondii* increases the concentration of dopamine in the brain (38). *Toxoplasma*-infected schizophrenia patients have more severe delusions and a reduced gray matter density in certain parts of the brain compared to *Toxoplasma*-free patients (38).

Autoimmunity

People with several autoimmune diseases have an elevated risk of developing schizophrenia, and *vice versa*. There are correlations between schizophrenia and many autoimmune diseases, e.g., multiple sclerosis, type 1 diabetes, celiac disease, autoimmune thyroiditis, autoimmune hepatitis, systemic lupus erythematosus, Crohn's disease, psoriasis, and Guillan–Barré syndrome (32). Multiple sclerosis and schizophrenia might even have similar pathogenetic mechanisms (15). Moreover, multiple sclerosis can at times predominantly present itself with psychiatric features (13).

Linking factors between schizophrenia and autoimmune diseases might be inflammatory events and their consequences (increased permeability of the blood–brain barrier and the intestinal wall, brain-reactive antibodies, increased levels of inflammatory cytokines, and primed microglia) (32). Another explanation might be a genetic vulnerability for dysfunctions of the immune system (32). The correlations between autoimmune disorders and schizophrenia fit well with the mild encephalitis hypothesis, which supposes autoimmunity as a possible trigger for mild inflammatory processes (12).

Autoimmune Encephalitis

Schizophrenia shares commonalities with autoimmune encephalitis, first described in 2008 (8). In autoimmune encephalitis, antibodies attack neural brain structures (9, 39). For example, anti-NMDA receptor encephalitis is caused by immunoreactivity against a specific part of the NMDA receptor (9, 39). The disease primarily affects females in early adulthood and is accompanied by a tumor in approximately 50% of cases, in this patient group (39). Healthy controls were also found to carry NMDA receptor antibodies, with increasing prevalence depending on age, making the presence

of antibodies insufficient for the diagnosis of anti-NMDA receptor encephalitis (40).

Nowadays, additional types of autoimmune encephalitis have been uncovered targeting different neurotransmitter receptors, channel complex associated proteins or other cell structures (39). A growing number of neural antibodies can be detected, due to improved laboratory methods (13).

In anti-NMDAR encephalitis, psychiatric features such as psychosis, confusion, and aggressive behavior are often predominant in the initial phase; hence, patients are initially treated in psychiatric facilities (9). However, as the disease progresses, neurological symptoms, such as tongue thrusting, cheek biting, sucking of lips, hyperkinesia, rigidity, involuntary, stereotyped movements, and spasms, increase. Late stages of the disease are characterized by decreased consciousness and dysregulation of the autonomic center with hyperthermia, elevated heart rate, and reduced breathing (39). Patients can often be treated successfully with immunosuppressive agents such as steroids, intravenous immunoglobulins, and plasmapheresis. Second-line therapy includes pharmacological agents used in cancer treatment and autoimmune disease (9, 39).

Endres et al. (41) found CSF and autoantibody abnormalities in 54.4% of 180 psychotic patients. Bechter (13) found that pathological measures (immunoglobulines, elevated cell counts, inflammatory cytokines, and blood-barrier dysfunctions) in CSF of 41% of schizophrenic and affective spectrum disorder patients, with lower level CSF abnormalities detected in 79% of severe, treatment-resistant cases. Several further studies investigated the prevalence of autoantibodies targeting neural structures in schizophrenia patients, psychiatric patients in general and controls, whereby the results are complex and difficult to interpret (40, 42–45). Presumably, the loss of blood–brain barrier integrity contributes to NMDAR antibody pathologies (40, 43). Antibody-associated mechanisms may be a transient phenomenon in schizophrenia (9), and the concurrent presence of autoantibodies is suggestive of a mild form of encephalitis syndrome (44). Antibody positivity may express itself as a continuum, ranging from relatively "pure" psychotic presentations to catatonia and potentially moribund encephalitis (44).

Just recently, in Germany, the death of a polar bear (ursus maritimus) of the Berlin Zoological Garden, received nation- and worldwide attention: the polar bear, called "Knut," drowned in 2011 due to seizures and was diagnosed with anti-NMDAR encephalitis post-mortem (46). Knut is the first non-human case of anti-NMDAR encephalitis. It received extensive media coverage and made autoimmune encephalitis known to the wider public.

Anti-inflammatory Drugs

The mild encephalitis hypothesis is reinforced by clinical studies finding therapeutic benefits when anti-inflammatory agents were added to the antipsychotic medication of schizophrenic patients (18, 20, 21). A meta-analysis of 26 randomized, placebo-controlled double-blind studies describes significant effects for aspirin, estrogens, and *N*-acetylcysteine (NAC, cough syrup) with low to moderate effect sizes (18). Estrogens seem to be effective only in female patients (16, 18); presumably, its effects are hormonal. No statistically significant effects are found for minocycline (antibiotic agent), and omega-3 poly-unsaturated fatty acids (omega-3 PUFAs) (18, 20, 21). However, these substances were shown to be effective in subgroups of patients, particularly in first-episode psychosis patients. Results for celecoxib [a selective cyclooxygenase-2 (COX-2) inhibitor] show a significant advantage in the same subgroup of patients (20, 47). Due to promising but inconclusive effects, further research on these and other anti-inflammatory drugs is necessary.

In a small pilot trial, Tocilizumab, an IL-6 receptor monoclonal antibody, was added to antipsychotics, showing positive effects on cognition without clinically significant side effects [(48), http://ClinicalTrials.gov identifier NCT01696929].

A recent Cochrane study reviewed the effectiveness of anti-glucocorticoid substances including 11 studies with 509 patients with psychotic disorders and found some positive effects for mifepristone, although the current data is insufficient to give clear recommendation (49).

A review on nutritional interventions summarizes clinical trials with adjunctive substances, such as antioxidants, vitamin B supplements, neuroprotective, and anti-inflammatory nutrients (alpha-lipoic-acid, melatonin, NAC, vitamin C and E, PUFAs, L-Theanine), as well as exclusion diets (casein-free, glutein-free diet). Based on the reviewed findings, the authors recommend personalized food supplementation, because this strategy could help detect and treat the nutritional deficiencies and food intolerances often encountered in patients. Furthermore, nutritional supplementation could ameliorate symptoms of schizophrenia in some patients (50).

Generally, the effect strength of anti-inflammatory drugs is shown to be greater in first-episode psychosis patients (18). This supports the assumption that inflammatory processes play an important part mainly in the early phase of mild encephalitis schizophrenia.

However, most of these drugs not only exert anti-inflammatory effects, but have further effects that might additionally or alternatively explain their efficacy in schizophrenia: (1) influences on the transmission of dopamine (estrogens, NAC), glutamate (NAC) or serotonin (omega-3-PUFAs), (2) effects on the gut microbiota (minocycline), (3) influence on the body's stress system (aspirin), (4) neuroprotection (omega-3-PUFAs), (5) enhanced neurogenesis (omega-3-PUFAs), and (6) influence on the composition of cell membranes (omega-3-PUFAs) (16, 18, 21, 51).

Inflammatory Status in Other Psychiatric Disorders

Inflammatory events could also play an important part in the development of bipolar disorder, major depression, and obsessive–compulsive disorder (21, 33, 52–55). Furthermore, neuroinflammation potentially contributes to neurodegenerative diseases, such as Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis, and frontotemporal dementia (56). Some forms of autoimmune encephalitis can even mimic Alzheimer's disease (57, 58).

Patients with mood disorders suffer more frequently from autoimmune disorders, e.g., multiple sclerosis and diabetes

(3-fold higher prevalence), rheumatoid arthritis, systemic lupus erythematosus, and inflammatory bowel disease (33). For example, bipolar disorder is accompanied by several systemic chronic diseases, such as artherosclerosis, hypertension, diabetes, and obesity, which are triggered by inflammatory processes (53). Anti-inflammatory agents (COX-2 inhibitor, acetyl-salicylic acid, fatty acids, and minocycline) are therapeutically effective in patients with bipolar disorder and major depression (33).

Schizophrenia as a Systemic Disease

According to the mild encephalitis hypothesis, schizophrenia is a systemic disease with preferential involvement of the brain rather than an exclusive brain disease (12, 20, 53). The link between pathologies both in the brain and in the residual body could be the CSF. CSF is produced by the choroid plexus, fills the ventricles and the area around the spinal cord, flows along cranial and spinal nerves, and comes into contact with muscular, subcutaneous, and peripheral neural tissue (12). In 41% of schizophrenic and affective spectrum disorder patients, CSF showed pathological signs (immunoglobulines, elevated cell counts, inflammatory cytokines, and blood-barrier dysfunctions), and 79% of severe, treatment-resistant cases had CSF abnormalities of low level degree (13). Inflammatory messengers likely spread *via* the peripheral cerebrospinal outflow pathway from the CNS to peripheral body compartments. This mechanism could also explain sensory hallucinations experienced by many patients (12). In a study of 180 psychotic patients, 54.4% displayed CSF and autoantibody abnormalities (41).

The understanding of schizophrenia as a systemic disease is further upheld by research on the gut microbiome: inflammatory bowel diseases, such as ulcerative colitis, Crohn's disease, and irritable bowel syndrome, have a more than 10-fold higher incidence in schizophrenia patients (3.4%) compared to controls (0.3%) (59).

Furthermore, the microbiomes of the oropharynx, pharynx, and intestinal organs differ between schizophrenia patients and controls (59, 60). By profiling oropharyngeal microbiomes with metagenomic sequencing, patients with schizophrenia can be distinguished from controls (60). Hence, a biomarker based on gut microbiota is conceivable (59, 60), and research in this area might facilitate the development of a laboratory test for schizophrenia.

ETHICAL ISSUES OF THE MILD ENCEPHALITIS HYPOTHESIS

If the mild encephalitis hypothesis was further strengthened by clinical evidence, major consequences would have to be expected for (1) the theoretical conceptualization of schizophrenia, (2) the appropriate medical discipline for schizophrenia, (3) the diagnostic procedures, (4) the treatment, (5) the pharmaceutic industry, (6) compulsory treatment, (7) the patients' social inclusion, and (8) the stigmatization of patients and their relatives.

In the following, we analyze the expected consequences ethically.

Theoretical Conceptualization of Schizophrenia

The diagnostic term "schizophrenia" can be compared to the umbrella term "bellyache," for didactic purposes. Rather than delineating certain organs, functional units, and mechanisms that cause the characteristic symptoms, its definition is based solely on symptoms, regardless of their possible causes (4). In an analogous way, the umbrella term "bellyache" describes pain in the abdomen, regardless of its anatomical position, e.g., gastrointestinal tract, Fallopian tube, or the liver, and regardless whether it is caused by infection, autoimmune processes, or poisoning.

Since schizophrenia is not a disease entity, but an umbrella term for different pathologies with common symptoms, subgroups of schizophrenia are feasible; e.g., "schizophrenia should be deconstructed" (61). One subgroup may be caused by mild encephalitis.

For a diagnosis of schizophrenia, DSM-5 requires that the disturbance is not attributable to "another medical condition" (criterion F). Defining "bellyache" analogously, this term could not be used as soon as the pain was attributable to a disorder of the stomach listed in DSM or ICD. The DSM-definition of schizophrenia makes it nearly impossible to explain schizophrenia by reducing the disease to a biological mechanism, since any mechanism would be considered "another medical condition." This would automatically exclude the diagnostic term: "schizophrenia." For example, if a patient is diagnosed with mild encephalitis (or, in fact, any other organic pathology), a diagnosis of schizophrenia can no longer be applied (44). Although mild encephalitis is not yet defined as a disease in the ICD-10, it would supposedly be considered a "medical condition" as soon as it was acknowledged that it can cause symptoms of schizophrenia. From that point on, the diagnosis "schizophrenia" could no longer be applied to patients with mild encephalitis.

The psychiatric classification systems DSM-5 and ICD-10 have often been criticized as "descriptive taxonomy based on expressed feelings and observed behavior" (62), as being agnostic on the etiopathogenesis of disorders (63), since its diagnostic tools are insufficiently based on a biomedical understanding of mental illness ((64)). The etiology of psychiatric disorders cannot be elucidated by psychopathology itself (13). The nominalistic approach of the DSM also poses an obstacle for research, slowing the progress of psychiatric science. For example, one reason for the lack of reliable biological tests for psychiatric disorders is the dependence of research criteria on the often too superficial DSM criteria (63).

The Research Domain Criteria (RDoC) project of the National Institute of Mental Health is being developed as an alternative classification system to the DSM-5 system, especially for researchers. The aim of this project is to classify mental disorders based on dimensions of observable behavior and neurobiological measures, e.g., genes, molecules, cells, circuits, physiology, behavior, and self-reports (63, 65). The RDoC could set the foundation for a classification system in which descriptive taxonomy is supported by a biomedical understanding of mental illness. This would further reduce the concerns that psychiatry is merely a tool for social control (64). The main elements of the mild encephalitis hypothesis of schizophrenia could be easily integrated into

appropriate RDoC sections, particularly the sections "molecules," "cells," and "physiology."

The Appropriate Medical Discipline for Treating Schizophrenia

The question of the medical discipline in charge of psychotic patients has far-reaching consequences for the diagnosis, treatment and life-long health care of patients. If patients do not present hard neurological signs such as epilepsy or movement disorders, they are normally hospitalized in psychiatry and diagnosed according to DSM-5 or ICD-10. Many psychiatrists do not routinely perform full physical examinations, since they are less aware of somatic causes of mental illness. Somatic illness is usually addressed as comorbidity, instead of being seen as a symptom of schizophrenia. Only if patients present hard neurological signs, they are referred to neurology, where they undergo CSF analysis, EEG, anti-neural antibody titer analysis, and brain imaging.

This kind of differentiation can become precarious, e.g., for patients with anti-NMDAR encephalitis. Initially, and sometimes throughout the whole course of disease, they may exclusively present psychiatric symptoms and are consequently hospitalized in psychiatric hospitals (9). Since blood tests and CSF analysis for anti-neural antibodies are not standard diagnostic tools in most psychiatric clinics, these patients are at risk of being diagnosed with schizophrenia. As a result of ineffective treatment, they might suffer severe, permanent brain damage or die. Indeed, several cases of patients with anti-NMDAR encephalitis and misdiagnosed with schizophrenia have been reported (42). Somatic examination and adequate antibody screening should become standard procedure in first-episode psychosis patients in order to find possible organic causes (9, 52, 54, 55, 66).

We recommend treating psychotic patients primarily in interdisciplinary teams, optimally in neuropsychiatric units. Psychiatric expertise is necessary for adequately dealing with severe behavioral symptoms and for psychotherapeutic treatment. Neurological expertise is necessary for CSF analysis, imaging data, and further neurological examination in order to adequately identify treatable organic causes (9, 13). Knowledge from both disciplines is needed for optimal, personally tailored pharmacotherapy. Causal therapies might target, e.g., teratomes, parasites, infectious agents, or autoimmune processes. Treating mental illness continuously over longer periods of time is especially challenging since symptoms, such as denial of illness, paranoia, irrational thoughts, deficits in executive function, and disruptive behavior, are often complicating factors (4). Therefore, it is of great importance that patients in early stages of the disease swiftly receive interdisciplinary diagnostics followed by appropriate, possibly causal, treatment.

If more evidence in favor of a mild encephalitis component in schizophrenia was gathered, the diagnostic procedure for patients with psychotic outbreaks would have to change significantly. Three different developments are possible: first, the responsibility for patients with schizophrenia would shift from psychiatry to neurology as it has happened with dementia. Second, the mild encephalitis hypothesis of schizophrenia would contribute to a reunion of psychiatry and neurology. Third, it would support interdisciplinary treatment concepts for schizophrenia.

In addition to psychiatrists and neurologists, internists, and when necessary experts for endocrinology, diabetology, and cardiology should be consulted for somatic comorbidities of schizophrenia, e.g., hypertension, obesity, diabetes mellitus, nicotine dependence, and dyslipidemia. This is of particular importance since physical illnesses are mainly responsible for the twofold to threefold increased mortality rate (25).

To reduce these high mortality rates of patients with schizophrenia and to adequately address their special medical condition, an integrated service provision is required (67). The coordination of mental and physical treatment could be managed by care coordinators (25, 67). Compared to standard care, patients in comprehensive community care settings showed better clinical and functional outcomes (68).

Diagnostic Procedure

As traditional classification systems such as DSM or ICD will not undergo radical change in the near future, biomedical tests should be added to the existing diagnostic schemes. A first example is the biomarker for schizophrenia based on the gut microbiota (59, 60). Progress in genomics, medical imaging, molecular biology, and cognitive sciences could aid in the development of reliable tests to accurately diagnose psychiatric disorders and to predict treatment response to specific drugs (4, 20, 62, 64). Several diagnostic procedures are recommended based on the mild encephalitis hypothesis.

The International Encephalitis Consortium recommends methods such as the investigation of CSF and serum, MRI, EEG and neurologic examination for diagnosing acute encephalitis (69). However, for mild encephalitis, a standard diagnostic procedure does not yet exist, because relevant changes in disease indicators are small and unspecific, making it difficult to set cut-offs and to detect pathologies (12). Nevertheless, standard diagnostic procedures for acute encephalitis could be adopted for mild encephalitis.

For detecting acute encephalitis, it is recommended to test paired CSF-serum samples for routine parameters, infectious agents, autoantibodies associated with autoimmune encephalitis, and immunoglobulins (69). Similarly, the gold standard for diagnosing schizophrenia of the mild encephalitis type is the investigation of CSF, since it allows the detection of even minor pathological abnormalities (12, 13).

CSF and Serum Investigation

Cerebrospinal fluid investigation is the most precise method for detecting inflammation in the central nervous system (13). Although it is not recommended in most guidelines, there are strong arguments for a systematic CSF screening of psychotic patients, especially prior to initiating psychopharmacological treatment (13, 41). With the help of CSF analysis, most neurological disorders can be excluded (13). However, lumbar puncture is not without risks. The most frequent complication is headache (36.5–60%). Rare complications are brain herniation, cardiorespiratory compromise, local or referred pain, hemorrhage, subarachnoid epidermoid cyst, and CSF leak. Serious adverse events

caused by infectious agents (e.g., meningitis) occur in <1% (70). When comparing the medical risks and the financial cost with the benefits of routine lumbar puncture in psychotic patients, the benefits overweigh, especially since CSF analysis offers the possibility for an effective, causal treatment.

Autoimmune Encephalitis

Each patient with psychosis should be tested for autoimmune encephalitis *via* routine screening for antibodies and inflammatory parameters in serum and CSF, particularly in a first-episode psychotic outbreak. This is necessary to avoid misdiagnosis and consequent inappropriate treatment possibly resulting in long-term disability or even death (41, 66). Patients with pathogenic antibodies can be detected only by screening all first-episode psychosis patients for antibodies (45). With the help of improved laboratory methods to measure antibodies, an increasing number of neural offenders will become detectable (13).

Red flags in the psychopathological status clinically pointing to autoimmune encephalitis, are movement disorders, disturbed consciousness, hyponatriemia, a rapid disease progression, catatonic symptoms, comorbid autoimmune diseases (Hashimoto thyroiditis), focal neurological deficits, MRI-, CSF- and EEG abnormalities, and a very acute disease onset (13). Since not all relevant autoantibodies are known yet, autoimmune encephalitis may be present even if tests for all known autoantibodies are negative. In this case, brain biopsy might confirm autoimmune encephalitis (52).

Disease-specific antibodies for schizophrenia have neither been found in serum nor in CSF (39). In a minority (8%) of schizophrenia patients, NMDAR antibodies are detectable, although they differ from those required for a diagnosis of anti-NMDAR encephalitis (44). These autoantibodies were found in patients with a first episode of psychosis, but not in chronic patients (44). Most likely, autoantibody-associated mechanisms are a transient phenomenon in schizophrenia (9). The presence of autoantibodies in some patients with schizophrenia suggests that these patients have a mild form of encephalitis (44). Whether an individual develops only psychotic symptoms or the full encephalitic syndrome may depend on several factors such as antibody subtype, antibody titer, brain area affected or blood-brain barrier integrity (40, 44).

Brain Imaging

In acute encephalitis, MRI can assist to detect abnormalities, demyelination or necrotic lesions, helping to illuminate the pathogenesis (39, 69). However, in mild encephalitis, MRI is not sensitive enough to reliably detect minor lesions and inflammation (12). Nevertheless, signs of mild atrophy, minor local intensities or local swelling could indicate states of mild inflammation (12). Fluorodeoxyglucose positron emission tomography is an important screening tool for yet undetected, but underlying tumors such as teratomas or lymphomas, which can produce antibodies causing psychosis (39). Furthermore, with the advanced dynamic contrast-enhanced MRI, blood-brain barrier disruptions can be investigated (40). Due to good availability and low side effects, neuroimaging is an appropriate method for excluding major brain pathologies (13).

Treatment

Since the pathophysiology of schizophrenia is still unknown, curative treatment or preemptive interventions are missing (4). Current treatments provide control rather than cure (5). The mild encephalitis hypothesis could change the treatment of schizophrenic patients considerably.

Reducing inflammation is the most important therapeutic consequence of the mild encephalitis hypothesis. It is the prerequisite for controlling both mental symptoms and the comorbidity "metabolic syndrome," which itself is also associated with mild and chronic inflammation (17, 20). Several treatment strategies are under investigation.

Food Supplements

Fishoil (omega-3 PUFAs) might be a preventive drug for patients with a high risk for developing schizophrenia. In a randomized, double-blind, placebo-controlled trial with high risk individuals aged 13–25, intervention with omega-3 PUFAs reduced the risk of progression to psychosis as well as psychiatric morbidity (follow-up 6.7 years). Only about 10% (4/41) in the omega-3 PUFA group transitioned to psychosis, compared to 40% (16/40) in the placebo group (5). Additionally, omega-3 PUFAs reduced positive and negative symptoms, and improved functioning compared to placebo (5, 51). The number needed to treat was 4, which is comparable to atypical antipsychotics (51). The effectiveness of omega-3 PUFAs has also been confirmed for (major) depression by a large meta-analysis (71). Omega-3 PUFAs are key components of brain tissue and, therefore, essential for neural development and function. Presumably, they influence membrane fluidity, receptor responses and modulate dopamine, noradrenaline, and serotonin levels (51). Furthermore, they have anti-inflammatory and anti-apoptotic potential (5). Possible side effects of omega-3 PUFAs, concerning the gastrointestinal tract, are only mild. The advantages of omega-3 PUFAs are their excellent tolerability, public acceptance, relatively low costs, and benefits for general health (21, 51).

Additionally, food supplementation with Vitamine C and *Ginkgo biloba* showed significant effects compared to placebo (20, 72).

Anti-inflammatory Medication

Anti-inflammatory medication seems to effectively target the underlying inflammatory states present in a subgroup of patients with schizophrenia (12, 17, 18, 20, 21, 47). Add-on of this treatment regimen was found to be most effective in first-episode psychosis and influenced by the initial inflammatory status of the patient. Therefore, anti-inflammatory medication could be a cause-targeted therapeutic strategy in early phases of the disease to stop its progression (16, 21).

Nevertheless, undesirable side effects have to be considered: aspirin can cause gastrointestinal bleeding; a complication to be avoided by adding gastric protection (16, 18). All in all, the benefit–risk ratio for aspirin is in favor of the prescription (21). NAC (cough syrup), has negligible side effects and offers specific benefits: it can be administered during pregnancy, and might reduce substance abuse, a frequent comorbidity in patients (22).

This makes NAC ideally suited as the first-line anti-inflammatory agent against schizophrenia (16, 18).

Celecoxib has rare but severe cardiovascular and gastrointestinal side effects, and should therefore be administered only in acute episodes rather than as long-term medication (21). Minocycline, though positively evaluated in animal and laboratory studies, cannot be recommended as first-line add-on agent because of its unclear efficacy and its significant risks (18, 20, 21).

At the moment, it is difficult to draw strong conclusions about the efficacy and safety of anti-inflammatory agents (16). Thus, no recommendations can be made in general (13). From an ethical point of view, NAC and aspirin can be recommended because of significant effectiveness and good tolerability; omega-3 PUFAs can be recommended because of a good benefit-risk ratio. Two patient groups might especially benefit from add-on of anti-inflammatory medication: schizophrenic patients with predominant immune alterations, and second, first-episode psychosis patients (16, 61). These two patient collectives should be included in future studies as a first step toward personalized medicine for schizophrenia (16, 20, 61).

Ongoing clinical studies include, e.g., studies on aspirin (http://ClinicalTrials.gov identifier: NCT02685748; NCT02047539), Siltuximab (IL-6 monoclonal antibody, NCT02796859), Tocilizumab (IL-6 receptor monoclonal antibody, NCT02874573), and L-tetrahydropalmatine (dopamine antagonist, NCT02118610), *Withania somnifera* (immunomodulator and anti-inflammatory agent, NCT01793935). Trials adding substances to conventional therapies are under current investigation, with promising results, e.g., statines, metotrexate (immunosuppressive and anti-inflammatory agent), glucocorticoids, ibuprofen, and salsalate (non-steroidal anti-inflammatory drug) (20).

Antipsychotics

Apart from their evident anti-dopaminergic characteristics, antipsychotics might be effective in schizophrenia due to their anti-inflammatory properties (16, 17, 33). However, many patients refuse antipsychotics due to side effects, particularly in the long run (28, 51, 64). Since the benefit-risk ratio of antipsychotics is unsatisfactory, they should be administered for the shortest time and the lowest dose necessary to avoid severe side effects (6).

CSF Filtration

Cerebrospinal fluid filtration could be an add-on therapy in severe therapy-resistant schizophrenic and affective spectrum psychoses with immunological genesis (11). The risks of CSF filtration are justifiable in light of the reduced quality of life and high suicidal risk of psychotic patients (11).

Consequences for the Pharmaceutic Industry

Current pharmacological treatment options for schizophrenia (mainly antipsychotics) are merely symptomatic, not curative, with limited effectiveness and tolerability. They cannot improve functional recovery, and relapse rates are still about 80% (4). Therefore, better drugs are urgently needed. In agreement with the mild encephalitis hypothesis, drug development focusing on suppressing inflammatory processes might finally open the door to curative treatment.

The main challenge in developing an appropriate anti-inflammatory agent is the agent's ability to pass the blood–brain barrier.

Current available agents known to cross the blood-brain barrier include: antipsychotics, celecoxib, estrogens, omega-3-PUFAs, minocycline and NAC (18). Aspirin, monoclonal antibodies, and corticosteroids are less able to reach the CNS (18). Despite varying treatment response, older, existing anti-inflammatory drugs with expired patent protection (e.g., NAC, aspirin, celecoxib) could partly replace the more expensive antipsychotic drugs. As there is little incentive for research on old drugs with expired patent protection or cheap food supplements (e.g., omega-3 PUFAs, fishoil), further drug development will likely have to be state-funded.

However, as elaborated above, established anti-inflammatory drugs have a varying efficacy in schizophrenia, and entirely novel, more effective and well tolerable drugs are urgently needed. The demand for new, anti-inflammatory drugs would have significant impact for the pharmaceutical industry. The necessary research would be much more expensive than research on existing drugs. Therefore, depending on the economic and legal conditions of different countries, this research should be conducted by universities, and, if necessary, in combination with the pharmaceutical industry.

Compulsory Treatment

In response to the UN Convention on the Rights of Persons with Disabilities (73), many countries have modified their laws in order to protect psychiatric patients from being treated compulsorily. For example, the German Federal Constitutional Court acknowledged the "freedom to be ill" in several court rulings on forensic patients, diagnosed with schizophrenia, resisting compulsory treatment with antipsychotics. Besides these individual decisions, the Court decided that the federal laws allowing compulsory drug treatment were unconstitutional. German state parliaments were urged to reformulate their civil commitment laws and implement stricter legal conditions for compulsory treatment. In particular, compulsory treatment was limited to patients incapable of consent; justified by the argument that the freedom to be ill must not be considered detached from the real capacities of free decision-making which may be limited by illness (74).

Although legislation in most Western countries increasingly gives priority to patient autonomy, the concept of autonomy is insufficiently elaborated on. Criteria for the legal concept of "free will" require further explanation. Particularly, input from neurobiology, psychiatry and philosophy is needed. It is important to note that certain psychiatric diagnoses do not exclude freedom of will. Tebartz-van-Elst (75) showed the extent to which free will depends on certain mental functions and those that can be compromised by brain diseases.

We are convinced that individual court rulings would have come to a different conclusion in light of the mild encephalitis hypothesis of schizophrenia, assuming successful treatment of schizophrenia with anti-inflammatory drugs in a relevant subgroup of patients.

First, the Court extensively cited the adverse side effects of antipsychotic drugs. In contrast, current anti-inflammatory drugs such as aspirin and NAC are considered harmless; thus, making a ruling in favor of compulsory treatment more plausible.

Second, the Court's decision was likely influenced by the fact that antipsychotics are merely a symptomatic, rather than a curative treatment for schizophrenia.

Third, the Court argued with the potential of antipsychotic medication to change the personality. Although it remained inconclusive with regard to the question whether schizophrenia is a psychosocial disorder or a genetically determined condition, as the disease was considered deeply ingrained to an individual's personality. If the Court adopted the understanding of schizophrenia as an acquired neurological condition, caused or triggered by viruses, parasites, tumors or autoimmune processes, it would not condemn curative drugs. Rather, these drugs would have to be considered *personality-restoring* drugs. Particularly, the involvement of the parasitic protozoan *T. gondii* in schizophrenia might be a convincing argument for the judges, as its survival strategy can be explained by the manipulation hypothesis (38): *T. gondii* is transmitted from intermediate hosts such as mice and rats to its definitive hosts, namely cats, by predation. Hence, *Toxoplasma* relies on cats to eat infected rodents. For facilitating the transmission from the intermediate to the definite host, the parasite manipulates the rodents in several ways: reaction times become prolonged, and the rodents specifically lose their fear to cat odor; this peculiarity is called the fatal attraction phenomenon. The same mechanism is probable in our next of kin: *Toxoplasma*-infected chimpanzees lose the fear to leopard urine (76). Toxoplasmosis can also cause similar behavioral changes in humans: it increases reaction times, resulting in higher probability of traffic and work accidents; additionally, infected men rated the smell of cat urine as relatively more pleasant (38). The suicide rate of infected mothers is twice that of non-infected mothers (77). According to the manipulation hypothesis, these changes could result from the fact that our distant ancestors were also part of the leopards' prey. In this context, schizophrenia cannot be seen as belonging to the core of the personality.

We expect that the threshold for allowing compulsory treatment would decrease, if legal theorists and high judges accepted the mild encephalitis hypothesis of schizophrenia and if anti-inflammatory drugs were more effective and had lesser adverse effects compared to antipsychotic medications.

However, we expect that the number of compulsory treatment would be reduced significantly in the long run: if patients made the experience that physicians could effectively help them overcome their suffering in the psychotic phases without experiencing the adverse effects of antipsychotics, many would be more compliant with long-term treatment (if necessary). Furthermore, they might sign psychiatric advance directives (Ulysses contracts) for allowing drug treatment in case of another psychotic episode, even against the psychotic will (78). Finally, the better medical treatments can cure the disease, the lesser compulsory treatments would be necessary at all.

We recommend the following: the will of an acutely psychotic individual most likely differs significantly from his or her free will. In a psychotic state, reality perception is largely disturbed; the affect is changed; anxiety and panic dominate, such that the power of judgment is corrupted. Particularly, thought intrusions corrupt the individual's free will. The affected person is not autonomous, and therefore lacks the capacity to give informed consent. Consequently, a proxy has to decide—but according to the affected individual's will: first, according to his or her formerly declared will (ideally in an advance directive), second, to his or her assumed will, and third (in case that the latter two are unknown), in his or her best interest.

As we have argued elsewhere (79), respect for autonomy is also a positive duty. If a person's capability for autonomy is corrupted by a disorder, respect for the person's autonomy means primarily to restore her capability for autonomy. If restoration of the capability for autonomy is possible with antipsychotics and/or anti-inflammatory medication, then it is a moral obligation to treat the person with these drugs. Once the capability for autonomy is restored, the patient can decide autonomously about his or her further treatment. However, if the patient has ruled out any of these treatments in an advance directive written in a state of legal competence, then this decision has to be respected, as well.

Social Inclusion

Until the 1970s, people with severe mental illness such as schizophrenia were treated in psychiatric hospitals in great numbers. Due to their often chronic conditions and missing treatment options, they spent most of their lives in sanitariums or asylums (67). With the deinstitutionalization process, the responsibility of care for people with chronic mental illness shifted from hospital- to community-based health services. However, the chronic and severe course of schizophrenia often leads to mental and medical disability, unemployment, homelessness and even incarceration (4). Throughout Europe, less than 20% of people with schizophrenia are employed, and in the USA, people with severe mental illness are three times more likely to be found in the criminal justice system than in hospitals (4).

If new, more effective treatments were developed on ground of the mild encephalitis hypothesis, many patients with schizophrenia of the mild encephalitis type could shift from being chronically ill and mentally disabled to being temporarily ill and treatable patients. Presumably, early interventions targeting underlying pathologies could prevent a chronic course of disease and cognitive impairment, enabling successful reintegration and participation in the community. However, it remains an open question as to how many patients could actually profit from these new therapeutic strategies.

Economically, employment of patients in remission can reduce indirect health costs, since the patient's productivity is no longer lost and family members can partly pursue their professions (80). Employment improves the patient's compliance and reduces hospital re-admission rates, which plays an important role in the patient's quality of life (80).

Stigmatization

Psychiatric disorders are severely stigmatized in both lay and professional settings (67, 81). Stigmatization means that people are classified and stereotyped due to a negatively connoted attribute. It is often associated with segregation, loss of social

status, discrimination in important contexts, and devaluation in a social hierarchy (82). Stigmatized individuals often develop self-stigmatization and withdraw from society. Stigmatization often includes the families of stigmatized persons (courtesy stigma) (83).

The question, whether biological explanations for psychiatric disorders reduce or increase stigma, has been discussed controversially for several decades.

The pessimistic fraction suspects that biologizing psychiatric disorders, particularly "genetic determinism," intensifies discrimination and stigmatization, because it increases feelings of fear and unfamiliarity (84). Since it assumes an inborn predisposition for deviant behavior, it strengthens the assumption that the disease is unchangeable, persistent, and hereditable (85).

The optimistic fraction is convinced that biological explanations reduce blame against persons with mental disorders, since it assumes that the main reason for stigmatization is the attribution of responsibility for the onset and/or maintenance of the deviant behavior. If a mental disorder is biologically caused, then the person is not responsible for the onset nor the offset or the resulting behavior of the disorder (85).

Empirical research on stigmatization has shown that biological explanations particularly increase stigmatization of diseases which are associated with perceived dangerousness and unpredictability (81). Furthermore, poor treatment success increases stigmatization. Hence, biological explanations might reduce stigmatization as soon as successful treatment options are available (86).

Schizophrenia is associated with (1) perceived high dangerousness and unpredictability, (2) high psychosocial disability and exclusion, and (3) poor treatment success. However, onset and offset responsibility is low. Indeed, it has been shown that stigmatization of people with schizophrenia increases due to biological explanations (86, 87).

The mild encephalitis hypothesis will probably affect stigmatization of schizophrenia in several ways: it does not support genetic determinism, but instead the concept of genetic vulnerability. Therefore, we expect that it will decrease stigmatization in comparison to mainly genetic explanations, but increase it compared to social explanations of schizophrenia.

With the mild encephalitis hypothesis, we do not expect a change concerning the attribution of onset responsibility. We expect a de-stigmatizing effect insofar as it offers some hope for better treatment strategies. Additionally, the patients' compliance might improve due to less adverse effects of effective drugs, thus, in the long-term, relapse rates might be reduced and cognitive functioning improved. This could decrease the perceived dangerousness and unpredictability of patients and improve their social inclusion. Furthermore, we expect reduced stigmatization of genetic relatives, if the influence of genes is seen not as a determination, but merely as a vulnerability factor.

Finally, we expect a major de-stigmatizing effect as soon as a multi-disciplinary approach in the treatment of schizophrenia is adopted, integrating psychiatry, neurology, and somatic disciplines.

The story of the popular German polar bear, Knut, might also contribute to destigmatization of schizophrenia because some empathy might be transferred from the bear to people suffering from psychosis.

In summary, we expect the mild encephalitis hypothesis to decrease stigmatization of patients with schizophrenia, provided effective drug therapies are developed based on biological findings. Novel therapies based on anti-inflammatory substances might help not all, but a significant number of patients with schizophrenia of the mild encephalitis type.

CONCLUSION

We cannot predict the further scientific development in psychiatry. Rather, we investigated the consequences of the mild encephalitis hypothesis of schizophrenia for the scientific community, and evaluated these consequences ethically. Most of these consequences are favorable from an ethical point of view.

Effective treatments of schizophrenia are urgently needed in order to reduce the burden for the patients, their relatives and society in general. For the development of effective treatment strategies, biological research on the etiology of schizophrenia is paramount. Research on both old and new drugs for treating mild encephalitis should be funded by public authorities. Increasing evidence supports the mild encephalitis hypothesis. Therefore, from both a scientific and an ethical point of view, further research on the role of inflammation in the etiology of schizophrenia and other psychiatric and neurological diseases is essential. Knowledge about the biological underpinnings of psychiatric disorders should be transferred into clinical research and clinical practice. Biological tests, particularly paired serum-CSF analyses, should become standard investigations for all psychotic patients in order to identify the appropriate treatment for the individual patient.

AUTHOR CONTRIBUTIONS

RR and SM have both contributed to the article with regard to development of ideas and definition of its contents and structure. RR conducted the literature search and evaluation. Both authors read and approved the final manuscript.

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How Will the Mild Encephalitis Hypothesis of Schizophrenia Influence Stigmatization?

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INTRODUCTION

People diagnosed with mental disorders, particularly those with schizophrenia, are severely stigmatized (1, 2). The image of people with mental disorders is strongly influenced by the mass media, which are then influenced by the prevailing medical opinion as well as by current research results. Therefore, researchers in psychiatry bear a certain responsibility for the stigmatization of their very own research objects.

Within the recent years, the mild encephalitis hypothesis receives more and more scientific interest. According to this hypothesis, a mild, but chronic, encephalitis underlies the symptoms of schizophrenia in a subgroup of patients. Infections, traumas, or autoimmune diseases can cause a mild encephalitis, which leads to psychiatric and/or neurological symptoms (3–5).

Since the mass media have recently started to report about the association of brain inflammation and schizophrenia, the mild encephalitis hypothesis is starting to influence the public's opinion about people diagnosed with schizophrenia, and thus will have a certain influence on the stigmatization. Whether it will increase or decrease stigmatization has not yet been investigated empirically. In the following, we discuss this question on grounds of theoretical concepts and empirical research on stigmatization of schizophrenia.

STIGMATIZATION OF MENTAL DISORDERS

Stigmatization is sociologically defined as the classification and stereotyping of people because of a negatively connoted attribute, together with segregation and loss of social status, discrimination in important contexts, and devaluation in a social hierarchy in a situation of exercise of power (6). Many stigmatized individuals internalize the negative evaluation, try to hide the negatively connoted attribute, and withdraw from society (self-stigmatization). Stigmatization often affects the social circle, particularly the families (courtesy stigma) (7).

Many biologically orientated researchers are convinced that biological explanations of psychiatric disorders will reduce stigma. This optimistic view is based on the attribution theory, assuming that the main reason for stigmatization is the attribution of guilt or responsibility for the onset and/or maintenance of the deviant behavior (8). Accordingly, biological, and particularly genetic, explanations should reduce blame against persons with mental disorders as soon as people understand that the strange or frightening behavior is not caused by evilness or weak will, but by a disease (9).

This conviction is contested by many social scientists. Because both the moral and the medical concepts assume an inborn predisposition for deviant behavior, a genetic explanation of deviant behavior does not diminish rejection (10). Genetic explanations assume mental disorders to be unchangeable, more serious, and hereditable (9, 11). People convinced of "genetic essentialism" believe that the genes are a person's essence and that the characteristics and behaviors of a person

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are based on his/her genetic makeup (11). Genetic explanations increase self-stigmatization (12) and courtesy stigma, particularly the stigmatization of genetic relatives of people with mental illness (9). Furthermore, this approach supports a paternalistic attitude towards mentally ill persons, questioning their autonomy and decisional capacity (13).

The attribution theory and the concept of genetic essentialism are not mutually exclusive; rather they grasp different aspects of stigmatization: the first one mainly the attribution of guilt and the second mainly the fear and the feeling of social distance (10).

EMPIRICAL RESEARCH ON STIGMATIZATION OF MENTAL DISORDERS

Empirical research supports the theory of genetic essentialism and widely disproves the attribution theory for major depression and schizophrenia. For example, a representative study with 1,241 participants (9) confirmed only one prediction of the attribution theory, namely, that people who are convinced of genetic explanations pleaded for lesser punishments for violent behavior of mentally disordered persons. However, there was support for predictions based on the concept of genetic essentialism. People who assume genetic causes of schizophrenia believe in a greater seriousness, tenacity, and pervasiveness of the deviance and hold more social distance against the siblings of mentally disordered persons.

A systematic review of population-based studies found that biogenetic beliefs about the cause of schizophrenia or depression were associated with greater social distance and thus stronger stigmatizing attitudes (1).

Based on the aforementioned and further studies on stigmatization, we have hypothesized that several factors influence whether a given biological model of a given psychiatric disorder will increase stigmatization: (1) disease-specific factors and (2) model-specific factors (10).

(1) Disease-specific factors: biological explanations increase the stigmatization of a given psychiatric disorder, as soon as people think that this disorder is associated with (a) high dangerousness/unpredictability, (b) high psychosocial disability, (c) poor treatment success, and (d) high responsibility for the onset and/or offset of the disease. Among these factors, the most important one is the perceived dangerousness/unpredictability, because this attribution leads people to seek social distance (2).
(2) Model-specific factors: there are different models of psychiatric disorders are, e.g., psychosocial models, the genetic model, the neurotransmitter disturbance model, or the mild encephalitis hypothesis. Model-specific factors can modulate the effects of disease-specific factors in various ways. Model-specific factors can influence the stigmatization, for example, the factor dangerousness/unpredictability either by changing the real dangerousness of people with this disorder or by changing the people's perception of the dangerousness. The first effect could take place if the model implied an effective treatment against psychosis and/or aggressiveness, the latter if the model convinced people that the disorder was not necessarily associated with dangerousness.

The differential effects of the model-specific factors might be contradictory. For example, genetic explanations of schizophrenia decrease the onset responsibility, but might squash hopes for successful treatments, at least in the laymen's perception.

Indeed, empirical research on the effects of different models on stigmatization has brought inconsistent results.

According to Rüsch et al. (12), the endorsement of genetic explanations was correlated with a stronger desire for social distance, whereas the endorsement of neurobiological explanations was not correlated with stigmatizing attitudes. In both cases, the attribution of responsibility was reduced.

According to Angermeyer et al. (14), the endorsement of a brain disease hypothesis is associated with increased anger and fear, which is associated with increased social distance. On the contrary, there was no significant association between the endorsement of hereditary factors and social distance, assumedly because the endorsement of hereditary factors increases on the one hand fear and on the other hand prosocial feelings.

In general, biological explanations of schizophrenia increase stigmatization, because schizophrenia has high degrees for three disease-specific factors (dangerousness/unpredictability, psychosocial disability, and poor treatment success). However, it remains an open question whether and in how far neurobiological explanations have a different effect on stigmatization as compared to genetic explanations. This situation is not only due to the inconsistent study results but also due to the rather crude biological explanations used in the studies.

ANTI-STIGMA MESSAGES

Accompanying research on stigmatization can contribute to a responsible psychiatric research that will not harm psychiatric patients by involuntarily increasing stigma. Empirical research on stigmatization of mental disorders is particularly necessary for communicating research results to the media and for designing anti-stigma campaigns which are not only well-intended but indeed beneficial for the concerned people. Since stigmatization is a multi-faceted phenomenon, interventions aiming at reducing stigma often have contradictory and unexpected effects.

According to a consensus paper on campaigns to reduce mental health-related stigma, the following message types should be used: (1) recovery-oriented, (2) "see the person," (3) social inclusion/human rights, and (4) high prevalence of mental disorders (15). Additionally, information on the continuous nature of psychopathological phenomena is recommended for anti-stigma messages (16).

INFLUENCE OF THE MILD ENCEPHALITIS HYPOTHESIS ON STIGMATIZATION

We expect that the mild encephalitis hypothesis will have different effects on the stigmatization of schizophrenia.

This hypothesis offers concrete hope for effective therapies with anti-inflammatory drugs for a subgroup of patients diagnosed with schizophrenia (17). Patients will probably accept these drugs better, so that their compliance will improve and the relapse rates might be reduced. With effective and potent drugs, many patients could be treated successfully, so that the dangerousness due to psychosis would vanish. Furthermore, their cognitive decline could be stopped, so that the level of cognitive functioning would be better. Diminished dangerousness and better cognitive functioning will positively affect on their social inclusion.

Because the mild encephalitis hypothesis contains no genetic determinism, but the concept of a genetic vulnerability, we expect that it will reduce the stigmatization of genetic relatives.

The mild encephalitis hypothesis might reduce the stigmatization further because it emphasizes the influence of infections and autoimmune disorders which can principally hit everyone, not only those with a special genetic makeup.

The mild encephalitis hypothesis might not influence the attribution of onset responsibility, because the patients are not responsible for any of the known causes of mild encephalitis. However, the attribution of offset responsibility might change significantly: if effective treatments without severe side effects were available, then the acceptance of the concept "liberty of illness" might diminish. People who refuse effective treatments will be considered as responsible for their enduring mental illness.

Finally, we expect that the stigmatization would be reduced significantly because the mild encephalitis hypothesis would support to shift the organizational authority over patients with schizophrenia from psychiatry to multi-disciplinary institutions combining psychiatry and neurology.

Therefore, we expect that the mild encephalitis hypothesis will contribute to a destigmatization of schizophrenia, of course particularly, if it will lead to effective drug therapies.

AUTHOR CONTRIBUTIONS

SM and RR have both contributed to the article with regard to development of ideas. SM wrote the first draft of the manuscript and developed the structure of the paper. Both authors read and approved the final manuscript.

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12. Lebenslauf

Mein Lebenslauf wird aus datenschutzrechtlichen Gründen in der elektronischen Version meiner Arbeit nicht veröffentlicht.

13. Komplette Publikationsliste

1. Müller, Riedmüller, Van Oosterhout: „Rivaling paradigms in psychiatric neurosurgery: adjustability versus quick fix versus minimal-invasiveness“, Frontiers in Integrative Neuroscience, 2015. 9:27. doi: 10.3389/fnint.2015.00027.

2. Müller, Riedmüller, Walter, Christen: „Ethical Evaluation of Stereotactic Neurosurgery for Anorexia Nervosa“, American Journal of Bioethics Neuroscience, 2015. 6:4, 50-65, DOI: 10.1080/21507740.2015.1094536.

3. Riedmüller and Müller: „Ethical Implications of the Mild Encephalitis Hypothesis of Schizophrenia“, Frontiers in Psychiatry, 2017. 8:38. doi: 10.3389/fpsyt.2017.00038.

4. Müller and Riedmüller: „How will the Mild Encephalitis Hypothesis of Schizophrenia influence stigmatization?“, Frontiers in Psychiatry, 2017. 8:67. doi: 10.3389/fpsyt. 2017.00067.

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