ISSN 2474-8927

SOCIAL BEHAVIOR RESEARCH AND PRACTICE

Open Journal

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Original Research

Repetitive Skin Focused Disorders May Express a Functional Connectome

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Article Information
Received: December 20th, 2018; **Revised:** January 8th, 2019; **Accepted:** January 8th, 2019; **Published:** January 19th, 2019

Cite this article
Reisz CM. Repetitive skin focused disorders may express a functional connectome. *Soc Behav Res Pract Open J.* 2019; 4(1): 1-7. doi: 10.17140/SBRPOJ-4-114

ABSTRACT

Background
Repetitive skin focused behaviors, such as nail biting, hair pulling, cutting, and others may involve brain regions that participate in visual and tactile awareness, contextual learning and anxiety.

Methods
Gender and age of onset were collected on 78 patients with a repetitive skin focused disorder from a general dermatology clinic between 2014-2018. The disorders included onychophagia (nail biting), trichotillomania (hair pulling), cutting, pathologic skin picking, acne excoriée (popping pimples) and delusions of infestations.

Results
Sixty/Seventy-eight, (77%) of the patients were female. Onychophagia, trichotillomania, and cutting emerged during key developmental milestones, such as adrenarche and pubarche. The 17 patients with delusions of infestations were middle-aged, between 52-66. Five/Seventy-eight (6%) attempted suicide, all female, three successfully.

Conclusions
Repetitive skin focused behaviors may reflect potentiation in neural circuits that participate in contextual processing, tactile and visual awareness. Trends emerged in gender predominance and age of onset. These disorders may have clinical utility in two key areas, emotional regulation in teenagers and drug toxicity in adults.

Trial Registration
UMKC IRB 16-464.

Keywords
Onychophagia; Trichotillomania; Delusions of infestations; Human connectome project; Locus coeruleus.

INTRODUCTION

Advances in neuroscience are occurring alongside wildly expanding clinical needs in depression and suicide, delirium and dementia.[1-4] Individuals contemplating suicide or harm to others are interfacing with health care systems that are either not recognizing those at risk or are not putting the riskiest patients in front of the clinicians with the greatest diagnostic acumen.[5-7] Clinicians rely on what the patient says, how they say it, and often include performance and cognitive measures to assign a diagnosis.[8-9] Many patients seen for routine medical exams have unrecognized needs for mental health care.

Altered patterns of self-grooming have been used to identify anxiety and obsessive-compulsive disorders (OCD) in animals.[10-12] Repetitive grooming behaviors are also seen in humans. Onychophagia (nail biting), trichotillomania (hair pulling), cutting and picking, repetitive piercing and tattooing, excessive use of cosmetic procedures, are common observations in clinical practice (Figures 1 and 2).[13-17] Repeated behaviors that involve the skin, especially those that leave marks or are accompanied by specimens, can be seen, graded and noted in the chart. In laboratory settings, neuroscientists have created maps of brain function and circuitry in task and non-task related situations.[18] Each hemisphere has been parcellated into regions defined by changes in

Figure 1. *Onychophagia in a Middle Aged Adult Male*

Figure 2. *Scars from Cutting on the Ventral Forearms*

Figure 3. *Diagram of Projections to and from the Locus Coeruleus*

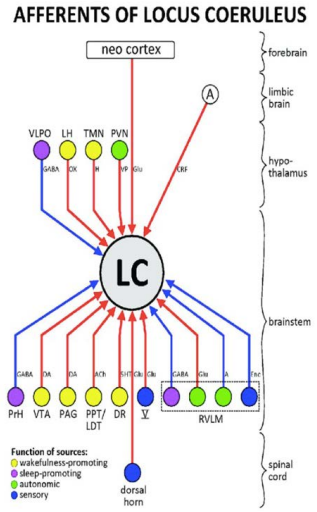
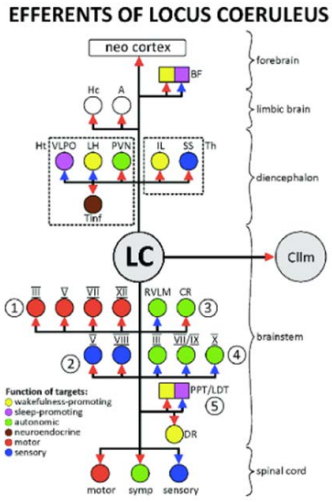


Figure 4. *Diagram of Projections to and from the Locus Coeruleus*



architecture, topography, connections, and function.[19-20] The study of fear conditioning has identified the brain regions that operate together to acquire memory and project that input to the amygdala and hippocampus for emotional processing.[21-24] The olfactory bulb functions as a relay station for environmental clues to admix with new neurons migrating from the dentate gyrus.[25-29] The locus coeruleus (LC), located in the pons, is a key hub in the governance of the noradrenergic system, and processes the physiologic changes clinicians see in anxious and alert situations (Figures 3 and 4).[30-34] Variation in heart rate and breathing, freeze and startle responses, pupil dilation, and blinking, sweat conductance in the palms, reflect the contribution of noradrenergic feedback on neural pathways.[34-39]

The LC receives input from over 100 regions in the nervous system and then projects to targets that activate the physiologic responses to the challenge.[30] The repetitive nature of the skin focused responses may accompany changes in the environment, phasic changes in hormones, fear, and memory-related tasks, and drug alteration in neurotransmitters. The development of fully characterized phenotypes around repetitive skin focused disorders may trigger clinical decision support in several areas; emotional well being in puberty, adults at risk for off-target drug effects and individuals with suicidal ideation.

METHODS

The patient data was obtained out of a general dermatology clinic between 2014 and 2018. The study was approved by the Institutional Review Board of the University of Missouri-Kansas City and in-

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formed consent was obtained from all participants included in the study. The patients presenting with trichotillomania and delusions of infestations used hair loss and sensations of animate material in the skin as their reason for a visit. The rest of the patients were enrolled after a repetitive skin focused behavior was observed during a routine clinical examination. When these findings were recognized, the nature of the study was presented to the patient and informed consent was obtained. The patients were informed that their data would be de-identified and would include age, gender, and age of onset. In addition, all patients with delusions of infestation underwent detailed histories of medical events, medication adjustments and the use of supplements. All material (specimen sign) brought in by the patient was examined under the microscope to document lack of an infestation. Sample: 78 patients were identified with a repetitive skin focused behavior. 60/78 (77%) were female. Onychophagia (n=19, 12/19 female), had the earliest presentation, between ages 3-8. Trichotillomania (n=20, 17/20 female) and cutting (n=9, 6/9 female) appeared between ages 12-14. Acne excoriée and picking (n=13, 12/13 female) emerged at two different points, ages 12-15 and 30-54. Delusions of infestations (n=17, 13/17 female) presented between ages 52-63.

RESULTS

Repetitive skin focused disorders are seen more commonly in women. All of the disorders, with the exception of delusions of infestations, had origins close to a developmental milestone (Figure 5). Eight/Seventeen (47%) of the patients presenting with delusions of infestations believed the infestation could be traced to a single event, such as exposure to mold, breaking glass or travel to a foreign country, suggesting overlap with fear conditioning. Within this group were trends towards polypharmacy and excessive use of supplements. A change in drug type or dose occurred around the time the delusion started in 9/17 (53%). Three/Seventeen (18%) had the same drug change, lisdexamfetamine to dexamphetamine/amphetamine. Other drug changes included continual adjustments in intrathecal bupivacaine and morphine; Simultaneous drug changes from amlodipine to losartan and fluoxetine to citalopram in one woman. Five/Seventeen (29%) patients were on opioids. Two/Seventeen disclosed illicit use of methamphetamine and hydrocodone. Seven/Seventeen (41%) were avid consumers of nutraceuticals (Table 1).

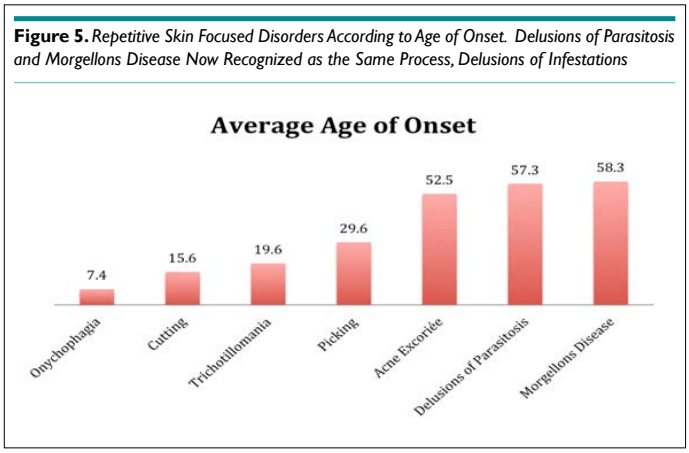

Figure 5. *Repetitive Skin Focused Disorders According to Age of Onset. Delusions of Parasitosis and Morgellons Disease Now Recognized as the Same Process, Delusions of Infestations*

Table 1. *Pharmaceutical and Supplement Data on 17 Patients with Delusions of Infestations*

Age of Onset	Gender	Associated Findings
52	Female	Ingestion of "all green super food" supplement product line
56	Female	polypharmacy (defined as 5 or greater drugs)
56	Female	Symptoms began after taking DHEA supplementation
63	Female	Polypharmacy in addition to varying doses in intrathecal pain pump
60	Female	Alcohol abuse and multiple anxiolytics
60	Female	Cutting her hand after dropping a glass plate. At time of injury, statin, SSRI and ARB, which continue
57	Male	Symptoms began after cutting from lisdexafetamine to dexamphetamine
63	Female	Solaray vitamin supplementation
45	Male	Work related fiberglass exposure near time of job loss. Ongoing methamphetamine and cocaine exposure
45	Female	Clonazepam, lisdexamfeatmine to dexamphetamine
44	Female	Sertraline, naltrexone. Symptoms began after sertraline doubled in dose.
54	Female	Testosterone injections at 48, bioidentical troches purchased off the internet, 8 additional supplements
49	Female	Effexor, metoprolol, positive urine drug screen for oxycodone
71	Female	Duloxetine, lisinopril, dexamphetamine, simvistatin, supplements. Started after coma after surgery complications at age 67
68	Female	Simvistatin, amlodipine: sensation started after change from lisinopril to amlodipine/olmesartan and did not resolve with cessation of olmesartan
45	Male	Specimen sign, dexamphetamine
53	Female	Specimen sign, armodafanil, esomeprazole, dexamphetamine, nucynta, apple cider vinegar, fish oil

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Five/Seventy-eight (6%) patients attempted suicide, all female, three successfully. The successful suicides were seen in women with extreme presentations of a repetitive skin focused disorder. These included near total scalp trichotillomania, the presentation of elaborate microscopic images of normal skin and hair clippings, and deep mutilating scars on the wrists. 4/5 of this group described multiple suicide attempts.

DISCUSSION

Clinicians need additional tools to assess risk for self-harm or the emergence of thoughts to hurt others. Many psychiatric and neurologic diseases proceed over a temporal continuum, an initial complaint or observable feature, viewed in isolation, may not register as a critical feature until additional and more severe expressions unmask the true potential of the problem. In a study of 571 suicides, 41% had sought health care within 4-weeks of their death, although far fewer disclosed their intent during the visit.[40-42] There is a similar problem with mass shooters. Often those closest to them have no idea of their plans.[43]

There may be aspects of the physical exam that would provide additional information to the provider on the emotional regulation of the patient, no matter the reason for a visit. The age of onset, gender, proximity to a developmental milestone or a medication change, could be key diagnostic features in a machine learning paradigm.[44] Seventy-seven percent of the patients in this series were female, suggesting that there may be gender differences in brain regions involved with emotion and perception (Table 2).[45-50]

Table 2. *Age and Gender of Patients with Repetitive Skin Focused Disorders*

Condition	N	Median Age of Onset	Onset Range	M:F	M:F%
Onychophagia	19	7	3-24	7:12	37:63
Cutting	9	15	14-18	3:6	33:67
Trichotillomania	20	15	6-54	3:17	15:85
Picking/acne excoriée	13	26	12-15 and 30-54	1:12	8:92
Delusions of Infestations	17	59	52-63	4:13	24:76

The effect of oral contraceptives and menstrual cycle phase on fear, memory, and anxiety remain largely unknown.[51-52] Women approach medical care differently, being open to taking prescriptions while also showing interest in natural approaches that include supplements and self-directed care.[53-54]

A review of classic drug-induced neurotoxic syndromes reveal specific vulnerabilities in the basal ganglia, the autonomic nervous system, and areas related to sleep, anxiety and thought.[55-60] The enzymatic oxidation of cholesterol to bile provides key metabolic functions, such as drug metabolism, the absorption of dietary lipids and protection of the endocrine system. Drug metabolism uses the same pathway as cholesterol catabolism. These pathways are inducible and can be compromised by age, illness, and co-ingestion with other medications.[61] The cholesterol-bile salt pathway is a frequent target of the pharmaceutical industry for diabetes, metabolic and cardiovascular disease.[62] Two commonly prescribed drug classes, HMG-CoA receptor antagonists (statins) and proton pump inhibitors (PPI's), were introduced in 1987 and 1990, respectively. Omeprazole, the first drug in this class to be introduced, inhibits the main efflux transporter in many organs, including the blood-brain barrier, permeability glycoprotein-1 (Pgp-1).[63] These two drug classes, statins and PPI's, are frequently seen in combination and impact the bile salt pathway and the receptors that govern drug clearance in ways that may not be predictable or recognized as an off target drug effect. Dopamine agonists, prescribed for Parkinson's disease and restless leg syndrome, can disrupt reward systems related to sex and gambling, although this is rarely brought up in the clinic.[64] Specialty visits usually focus on a specific outcome, and dose adjustments are made to performance measures of that outcome. Statins are adjusted for cardiovascular risk, Parkinson's medications titrated for tremor, additional adjustments are made for gastric reflux, bladder irritability, pain, and so forth, neglecting the balance of effect on other issues that may be of real importance to the patient.[65] Patients presenting with early drug-induced neurotoxicity syndromes tend to be exposed to a wide variety of medical practitioners including primary care providers, dermatologists, dentists, gastroenterologists, otolaryngologists, neurologists, psychiatrists. The common cause of injury (drug toxicity) is missed because each specialty is focusing on its specific dysfunction rather than the overall pattern.

Research on neural function has little uniformity and diagnostic categorizations do not scale across providers and researchers.[66-68] Our most basic clinical needs, the need to identify those at risk for self-harm and harm to others, are not being met. Repetitive skin focused disorders may reflect potentiated and possibly toxic communication between the thalamus, amygdala, locus coeruleus, insula, and hippocampus. The development of fully characterized phenotypes around repetitive skin focused disorders may provide a 'risk signature' that would scale across provider types.

CONCLUSIONS

There are missed opportunities in health care for individuals with mental health issues. Clinicians observe the manifestations of repetitive skin focused behaviors every day but may not know what to call it, how it should be factored into complex clinical presentations or whether the reason for a visit should be shifted to include emotional well-being. The development of fully characterized phenotypes around repetitive skin focused disorders may trigger clinical decision support in three key areas; mental health issues that emerge at puberty, adults at risk for polypharmacy and individuals with suicidal ideation.

CONFLICTS OF INTEREST

There was no funding obtained and the author has no financial conflicts of interest.

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