L-Dopa und DA-Agonisten: Einfluss auf Psyche und Cognition

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Informationstagung Parkinson Schweiz
20.10.2016

Bisher bekannte Therapien

Pharmakologie

- Dopamin
- Dopamin-Agonisten

Operation

- Tiefe Hirnstimulation

Psychologische Therapien

- Verhaltenstherapie
- Cognitives Training
- Anti-Stress-Training

Ergänzende Therapie

- Logopädie
- Physiotherapie
- Lichttherapie
- u.a.

Auswirkungen auf Alltag (I)

- Dopamin
  - Psyche
    - stimmungsaufhellend, sogar antidepressiv
    - Bei Reduktion: depressionsfördernd
    - Bei Überdosierung: Halluzinationen, Manien, Schlafstörungen, Psychose, Verfolgungswahn u.a.
  - Cognition
    - Cognitive Beschleunigung jedoch keine eigentliche Verbesserung kognitiver Defizite

Auswirkungen auf Alltag (II)

- DA-Agonisten
  - Psyche
    - Bei allen DA-Agonisten stimmungserhöhende Wirkung
    - Bei Pramipexol (Sifrol) gute antidepressive Wirkung bis zu mittelgradigen Depressionen
    - Nachgewiesene Förderung von Impulskontrollstörungen
  - Cognition
    - Keine expliziten Wirkungen bekannt

Impulskontrollstörungen (I)

- Impulskontrollstörungen (ICD)
  - Kaufsucht
  - Spielsucht
  - Esssucht
  - u.a.

Impulskontrollstörungen (II)

- Zwischen 7-14% aller Patienten unter DA-Behandlung
- Ursache nicht genau bekannt
- Hypothese
  - Dopamin-Rezeptor-Konfigurationsänderung durch Gabe von DA

Clinical Spectrum of Impulse Control Disorders in Parkinson's Disease

Daniel Weintraub, MD,[1,2*] Anthony S. David, FRCP, FRCPsych, MD, MSc,[3] Andrew H. Evans, FRACP,[4] Jon E. Grant, MD, MPH,[5] and Mark Stacy, MD[6]

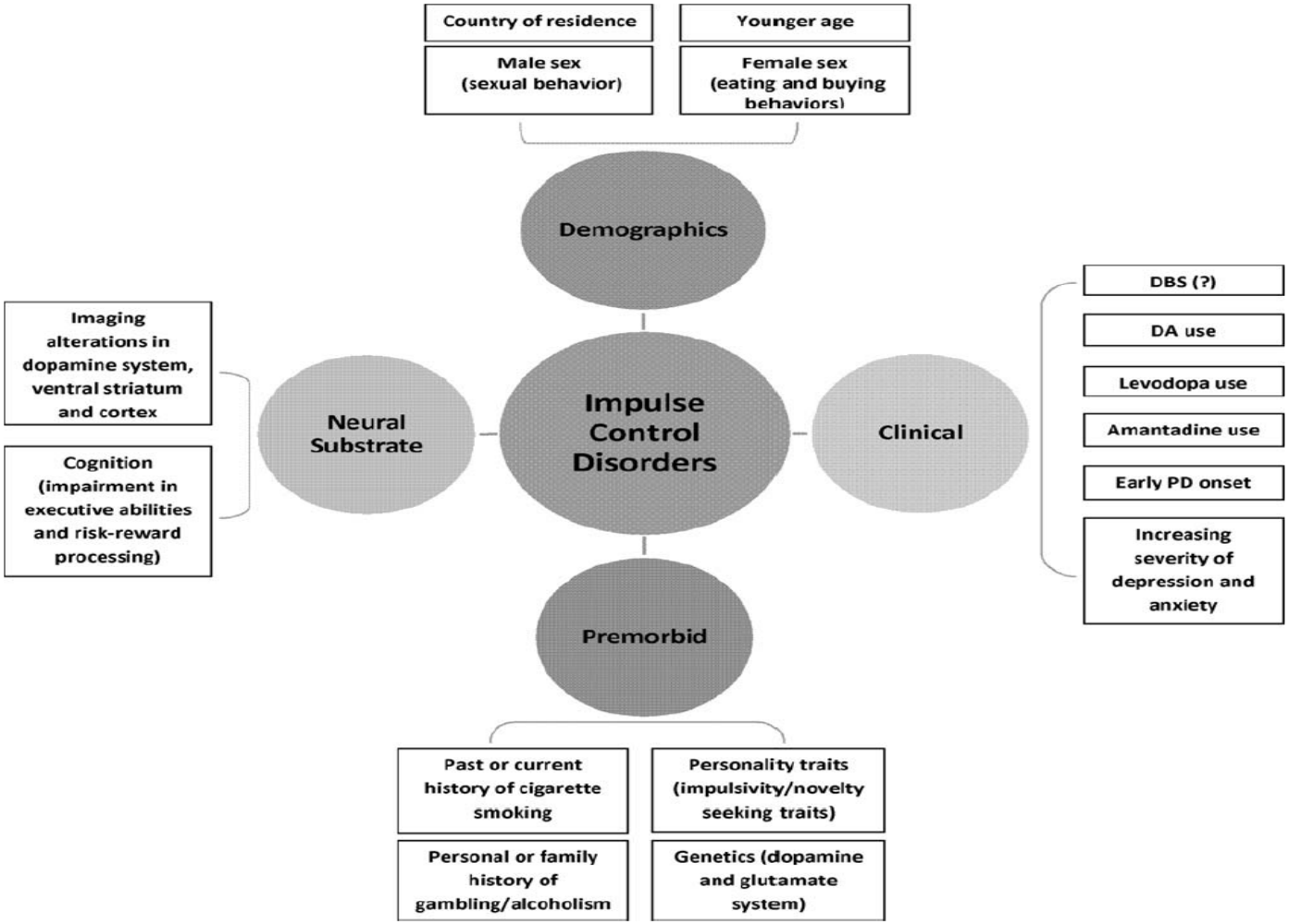


FIG. 1. Correlates and potential risk factors for ICDs and related behaviors.

Weintraub et al. 2015

ORIGINAL CONTRIBUTION

Impulse Control Disorders in Parkinson Disease

A Cross-Sectional Study of 3090 Patients

Daniel Weintraub, MD; Juergen Koester, PhD; Marc N. Potenza, MD, PhD; Andrew D. Siderowf, MD, MSCE; Mark Stacy, MD; Valerie Voon, MD; Jacqueline Whetteckey, MD; Glen R. Wunderlich, PhD; Anthony E. Lang, MD, FRCPC

Table 3. Multivariable Analyses of ICD Correlates in Entire Study Population

	All Subjects (N=3090)	
Variable[a]	**OR (95% CI)**	***P* Value**
Age, ≤65 vs >65 y	2.50 (1.98-3.15)	<.001
Not married vs married	1.48 (1.16-1.89)	.002
Living in the United States	1.62 (1.25-2.10)	<.001
Current smoking	1.70 (1.07-2.70)	.02
Family history gambling problems	2.08 (1.33-3.25)	.001
Dopamine agonist treatment	2.72 (2.07-3.57)	<.001
Levodopa treatment	1.51 (1.09-2.09)	.01

Abbreviations: CI, confidence interval; ICD, impulse control disorder; OR, odds ratio.

[a] Clinical and demographic variables included were those with $P<.10$ on univariate analysis; only data for significant results are presented.

Weintraub et al. 2010

Association of Dopamine Agonist Use With Impulse Control Disorders in Parkinson Disease

Daniel Weintraub, MD; Andrew D. Siderowf, MD, MSCE; Marc N. Potenza, MD, PhD; Joseph Goveas, MD; Knashawn H. Morales, ScD; John E. Duda, MD; Paul J. Moberg, PhD; Matthew B. Stern, MD

Table 3. Association Between Specific Dopamine Agonists and Active ICDs*

	No Dopamine Agonist Use†	Dopamine Agonist		
		Pramipexole	Ropinirole	Pergolide
Treated, No.	135	73	49	15
ICD cases, No.	0	5	3	3
ICD frequency, %	0	6.8	5.8	20.0

Sifrol

Requip

Abbreviations: ICD, impulse control disorder; PD, Parkinson disease.

*Pramipexole given as pramipexole dihydrochloride; ropinirole, as ropinirole hydrochloride; and pergolide, as pergolide mesylate.

†One hundred fourteen (84.4%) of 135 patients not taking a dopamine agonist were taking levodopa. The rest were taking other nondopamine agonist medications or no PD medications at all.

Weintraub et al. 2006

Auswirkungen auf Angehörige (I)

- soziales Umfeld:
  - Bei vorbestehender Depression und Dopamin- bzw. DA-Gabe bessere Kommunikation, mehr Lebensfreude, mehr Aktivitäten im Alltag, besserer Schlaf
  - Bei Überdosierung: Manien, Psychose, Impulskontrollstörung u.a.

Auswirkungen auf Angehörige (II)

- soziales Umfeld bei ICD:
  - Verschuldung, Partner-/ Arbeitsplatzverlust, schwierig zu kontrollierende psychosoziale Veränderungen (häufige Wohnungswechsel, schlechte Therapiecomplience u.a.)

Neue Therapie Ansätze (I)

- Education, Prävention, Überwachung
- Medikationseinstellung
- Psychiatrische Behandlung
- Psychologische Behandlung
- Tiefe Hirnstimulation
- Abwägen der DA-Entzugssymptomen vs. den Symptomen der ICD

REVIEW

CME

Management of Impulse Control Disorders in Parkinson's Disease: Controversies and Future Approaches

Michael Samuel, MD, FRCP,[1*] Maria Rodriguez-Oroz, MD, PhD,[2] Angelo Antonini, MD, PhD,[3] Jonathan M. Brotchie, PhD,[4] Kallol Ray Chaudhuri, MD, FRCP, DSc,[1,5] Richard G. Brown, PhD,[6] Wendy R. Galpern, MD, PhD,[7] Melissa J. Nirenberg, MD, PhD,[8] Michael S. Okun, MD,[9] and Anthony E. Lang, MD[10]

TABLE 1. Summary of treatment options for the management of impulse control disorders in Parkinson's disease (PD)

		Commentary
→ **Education, prevention, and surveillance**	Patient education, carer education, and surveillance to facilitate early diagnosis and treatment	Involvement of carers in surveillance for ICDs can facilitate earlier detection. Also, caregivers/family may participate in management when symptoms persist (if refractory or a patient needs to stay on causative drug(s) because of motor worsening or DAWS). Behavioral/environmental approaches, such as the removal of credit cards, limiting money expenditure, monitoring food intake, monitoring internet access, etc., can be considered on an individual basis.
→ **Adjustment of PD medications**	Reduce oral dopamine agonist - Observe for resolution of ICDs - Observe for loss of motor control - Observe for DAWS	As a class effect, dopamine agonists have a strong association with ICDs. Reduction to cessation of dopamine agonists (and substituting other PD medications, as needed) is the preferred treatment for ICD resolution, but may not be optimal for DAWS/motor control. Maintaining a low "sub-threshold" dopamine agonist dose—which might be effective at balancing the resolution of ICDs with worsening of motor control, or induction of DAWS—will continue to place a patient at risk of ICDs, with or without the influence of other factors, eg, if level of supervision decreases, other driving factors co-exist, other anti-parkinsonian medications increase, or covert ICDs are a possibility. All patients who continue dopamine agonist treatment—even at a low dose—need to be closely monitored for recurrent or worsening ICDs.
	If concomitant loss of motor control occurs as dopamine agonists are reduced, then consider adding a COMT inhibitor to the preexisting oral levodopa (L-dopa) doses, or increasing the L-dopa.	The effect of L-dopa is also associated with ICDs. No evidence of efficacy against DAWS.
	If concomitant loss of motor control occurs, consider adding an MAOI and observe for re-emergence of ICD	MAOI drugs can be rarely associated with induction of ICDs. No evidence of efficacy against DAWS
	Amantadine	Conflicting evidence about whether amantadine may be beneficial (for pathological gambling) or deleterious. Its use in ICDs is controversial.
	Consider switching from an oral dopamine agonist to transdermal rotigotine	Evidence is beginning to emerge, but currently is insufficient. Rotigotine has also been associated with induction of ICDs.
	Consider switching from an oral dopamine agonist to subcutaneous continuous apomorphine infusion	Evidence is beginning to emerge, but currently is insufficient. Subcutaneous continuous apomorphine infusion may fail to resolve ICDs and might potentially induce new ICDs.
	Consider switching to continuous intrajejunal L-dopa infusion to control motor symptoms.	Evidence is beginning to emerge, but currently is insufficient.

Samuel et al. 2015

REVIEW

CME

Management of Impulse Control Disorders in Parkinson's Disease: Controversies and Future Approaches

Michael Samuel, MD, FRCP,[1*] Maria Rodriguez-Oroz, MD, PhD,[2] Angelo Antonini, MD, PhD,[3] Jonathan M. Brotchie, PhD,[4] Kallol Ray Chaudhuri, MD, FRCP, DSc,[1,5] Richard G. Brown, PhD,[6] Wendy R. Galpern, MD, PhD,[7] Melissa J. Nirenberg, MD, PhD,[8] Michael S. Okun, MD,[9] and Anthony E. Lang, MD[10]

→ Psychiatric management	Consider addition of: - antidepressants - anxiolytics - atypical neuroleptics - antiepileptics - naltrexone	Psychiatric co-morbidity can occur with ICDs. Evidence for efficacy of psychiatric medications for ICDs is controversial. These drugs may help the psychiatric symptoms per se if they co-exist with ICD, and may help the ICD if the psychiatric symptoms are driving the ICD (eg, anxiety). Neuropsychiatric referral is suggested. Efficacy against DAWS is lacking.
→ Psychological treatment	Cognitive behavior therapy	Some evidence of efficacy in ICDs exists. Can also be tried for DAWS but evidence is lacking.
→ Deep brain stimulation	Consider "L-dopa–sparing" types of deep brain stimulation, such as at STN (or VIM if patient is mainly troubled by tremor)	Conflicting evidence as to whether STN DBS can improve ICDs or induce them. No clear conclusions can be drawn. DBS candidates may be inherently at higher risk of impulsivity. Postoperative surveillance for ICD, apathy, DAWS, and motor control is required. If ICDs are present postoperatively, consider the possibility of spread of current to adjacent structures, lead misplacement, or postoperative drug changes.
→ Consider the severity of DAWS vs. the severity of ICDs	Re-introduce dopamine agonist at the lowest possible dose to avoid DAWS	This will maintain the current ICD, and the future risk of worsening the ICD. Even patients whose ICDs initially improve may develop recurrent ICDs in the future. Marked caution is required. Consider whether ICDs or DAWS symptoms are the more distressing and the level of long-term surveillance required for ICDs.

Adjustment of PD medications—and reduction/cessation of dopamine agonists—is the primary treatment at this time; other treatments are unproven but can be considered. The order is not sequential. ICD, impulse control disorder; COMT, cathechol-O-methyl transferase; MAOI, monoamine oxidase inhibitor; DAWS, dopamine agonist withdrawal syndrome; STN, subthalamic nucleus; VIM, ventral intermediate nucleus; DBS, deep brain stimulation.

Samuel et al. 2015

Neue Therapie Ansätze (II)

- Falls Besserung der ICD durch Medikamenten-anpassung nicht möglich:
  - Sicherheitsmassnahmen: Konto-/ Internetsperre (nur in Absprache mit Arzt des Vertrauens)
- Falls keine medikamentösen Optionen auch Tiefen Hirnstimulationen erwägen

Movement disorders

RESEARCH PAPER

Incident impulse control disorder symptoms and dopamine transporter imaging in Parkinson disease

Kara M Smith,[1] Sharon X Xie,[2] Daniel Weintraub[3,4,5]

Table 5 DAT imaging predictors of incident ICD symptoms controlling for LEDD

	All participants		Participants on DRT	
	OR (95% CI)*	p Value	OR (95% CI)	p Value
Baseline DAT binding				
Right caudate	0.83 (0.42 to 1.64)	0.60	0.87 (0.44 to 1.75)	0.71
Left caudate	0.85 (0.48 to 1.52)	0.58	0.86 (0.47 to 1.59)	0.64
Right putamen	0.49 (0.13 to 1.87)	0.30	0.57 (0.15 to 2.16)	0.41
Left putamen	0.62 (0.21 to 1.77)	0.37	0.63 (0.21 to 1.88)	0.40
Mean total striatal	0.64 (0.24–1.74)	0.38	0.69 (0.25 to 1.94)	0.48
Change in DAT binding (baseline-year 1)				
Right caudate	1.58 (0.58 to 4.31)	0.38	1.67 (0.61 to 4.55)	0.32
Left caudate	0.98 (0.38 to 2.53)	0.96	1.00 (0.39 to 2.58)	1.00
Right putamen	0.66 (0.10 to 4.25)	0.66	0.75 (0.12 to 4.76)	0.76
Left putamen	1.44 (0.25 to 8.27)	0.68	1.54 (0.26 to 9.01)	0.64
Mean total striatal	1.29 (0.25 to 6.58)	0.76	1.43 (0.28 to 7.33)	0.67
DAT binding (post-baseline)†				
Right caudate	0.41 (0.17 to 0.95)	0.04	0.47 (0.19 to 1.19)	0.11
Left caudate	0.52 (0.20 to 1.37)	0.18	0.61 (0.22 to 1.73)	0.35
Right putamen	0.02 (0.002 to 0.21)	0.001	0.02 (0.001 to 0.18)	0.001
Left putamen	0.07 (0.01 to 0.56)	0.01	0.05 (0.01 to 0.40)	0.005
Mean total striatal	0.15 (0.04 to 0.56)	0.01	0.17 (0.04 to 0.71)	0.02

*Generalised estimating equations models for each variable controlled for baseline age and sex.
†Any post-baseline DAT binding value (time-dependent), assessed for association with incident ICD at the corresponding visit.
DAT, dopamine replacement therapy; ICD, impulse control disorder; LEDD, levodopa equivalent daily dosage.

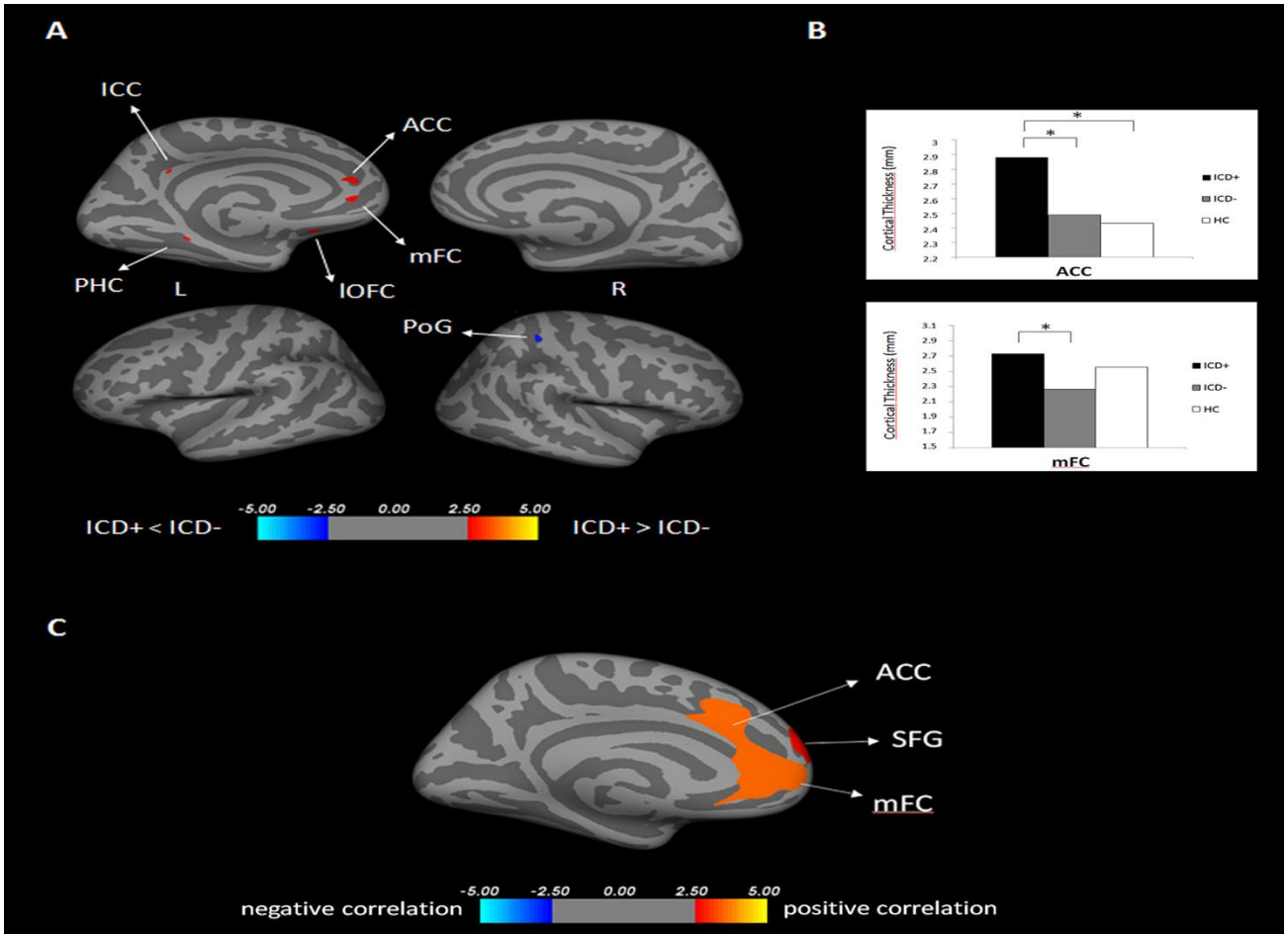
sig.

- DAT-Scan: Reduktion als Marker für Zukünftige ICD

Smith et al. 2015

Cortical thickness changes in patients with Parkinson's disease and impulse control disorders

Alessandro Tessitore [a, *, 1], Gabriella Santangelo [b, c, **, 1], Rosa De Micco [a], Carmine Vitale [c, d], Alfonso Giordano [a, c], Simona Raimo [b], Daniele Corbo [e], Marianna Amboni [d], Paolo Barone [f], Gioacchino Tedeschi [a, g]



- Messung der cortikalen Dicke:
  - Erhöhte cortikale Dicke cingulum, orbito-frontaler Cortex

Tessitore et al. 2015

REVIEW

Linking Neuroscience With Modern Concepts of Impulse Control Disorders in Parkinson's Disease

T. Celeste Napier, PhD,[1] Jean-Christophe Corvol, MD, PhD,[2*] Anthony A. Grace, PhD,[3*] Jamie D. Roitman, PhD,[4*] James Rowe, BM, PhD, FRCP,[5*] Valerie Voon, MD, PhD, FRCPC,[6*] and Antonio P. Strafella, MD, PhD, FRCPC[7]

Transmitter System	Protein	Gene/Allele	General Population	PD	References
Dopamine	DAT	*SLCA3*/VNTR	+	-	*Vallelunga et al., 2012*[88]
	DRD1	800 T/C	+	ND	
	DRD2	Taq1A	+	-	*Lee et al., 2012*[86]; *Vallelunga et al., 2012*[88]
	DRD3	P-S9G	+	+	
	DRD4	Exon3	+	ND	
Dopamine metabolism	COMT	Val158Met	+	-	*Vallelunga et al., 2012*[88]
	MAO-A	Promoter	+	ND	
Serotonin	Transporter	*SLC6A4*	+	-	*Lee et al., 2012*[86]
	Tryptophan hydroxylase	*TPH1*	+	ND	
	5HT2A receptor	*HTR2A*	+ (impulsivity)	+/− (trend)	*Lee et al., 2009*[88]
Glutamate	NMDA receptor	*GRIN2B*	+	+	*Lee et al., 2012*[87]

+, significant association with ICD; −, no significant association with ICD was found; ND, no data.

- Genetische Assoziation mit ICD, neben Dopamin auch Serotonin und Glutamat

Celeste Napier et al. 2014

Impulskontrollstörungen und neuere Forschungsbefunde (I)

Review

Dyskinesias and impulse control disorders in Parkinson's disease: From pathogenesis to potential therapeutic approaches

Haritz Jiménez-Urbieta [a,b,1], Belén Gago [a,b,1], Patricia de la Riva [c], Manuel Delgado-Alvarado [a,b], Concepció Marin [d], María C. Rodriguez-Oroz [a,b,c,e,*]

- «Abnormalitäten in Neurotransmittersystemen (z.B. Dopamin, Glutamat, Serotonin)
- → Funktionelle Änderungen des Gehirns (synaptische Plastizität)

Jiménez-Urbieta et al. 2015

Impulskontrollstörungen und Cognitive Verhaltenstherapie

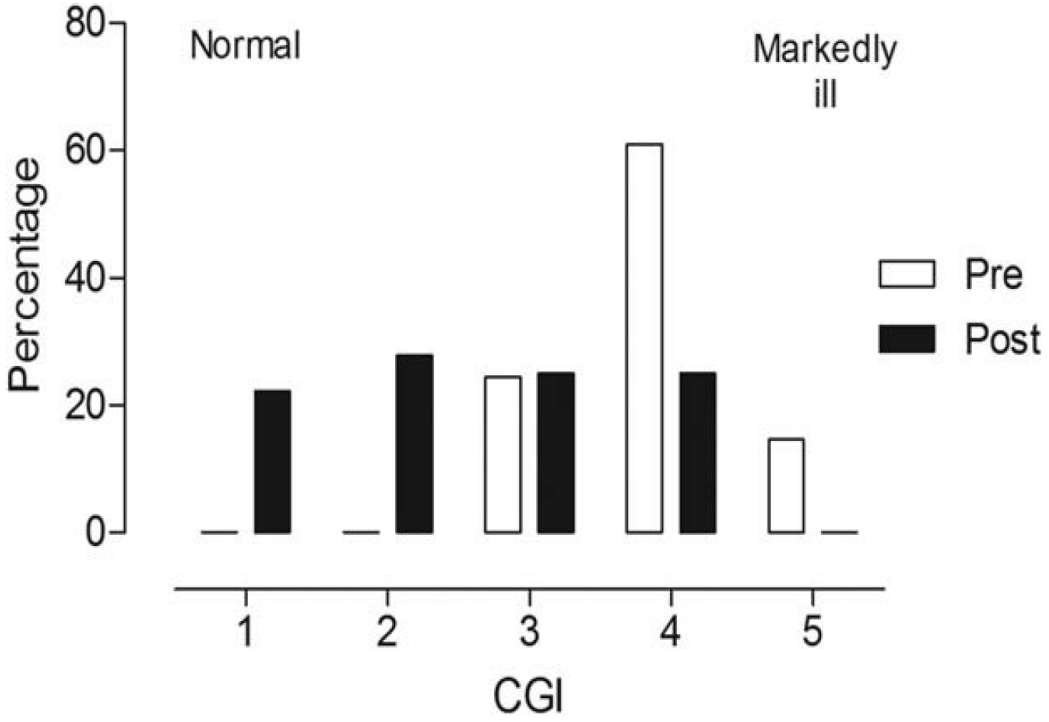


FIG. 1. Distribution of CGI scores pre and post treatment.

Predictors of Response to a Cognitive Behavioral Intervention for Impulse Control Behaviors in Parkinson's Disease

David Okai, MD,[1,2] Sally Askey-Jones, MSc,[1] Michael Samuel, MD,[3,4] Anthony S. David, MD,[1] and Richard G. Brown, PhD[5*]

Okai et al. 2015

MSc. Antonia Meyer

Rückmeldung: Anti-Stress Gruppentraining

Rückmeldung: Anti-Stress Gruppentraining

Interventionsgruppe **Cognitive Verhaltenstherapie (CVT)**	**Kontrollgruppe** **Health Enhancement Program (HEP)**
9 Sitzungen mit folgendem Inhalt:	9 Sitzungen mit folgendem Inhalt:
1. Selbstbeobachtung 2. Stressreduktion 3. Entspannung und Geniessen 4. Auswirkung der Krankheit 5. Trauer und Depression 6. Hilfe suchen 7. Rolle der Angehörigen 8. Beziehung zu den Angehörigen 9. Zusammenfassung	1. Kunsttherapie 2. Kunsttherapie 3. Physiotherapie 4. Physiotherapie 5. Physiotherapie 6. Ernährungsberatung 7. Ernährungsberatung 8. Medizinische Fragen 9. Zusammenfassung

Rückmeldung: Anti-Stress Gruppentraining

	Change score			
Fragebogen	**Cognitive Verhaltenstherapie** Mittelwert *(Standardabweichung)*	**Health Enhancement Programm** Mittelwert *(Standardabweichung)*	*p* - Wert	*Effektstärke* (η^2)
Belastungsfragebogen Summe	5.56 *(11.48)*	-2.75 *(9.36)*	**.026**[a]	.139
Fragebogen zur Krankheitsbezogenen Kommunikation	4.68 *(5.98)*	1.07 *(2.28)*	**.037**[a]	.118
Parkinson's Disease Questionnaire-39	5.31 *(13.94)*	3.25 *(6.30)*	**.030**[a]	.13

Verwendeter statistischer Test: Mehrfaktorielle Varianzanalyse (MANOVA).
Positiver Mittelwert impliziert einen Benefit durch das Training .
[a]Signifikanz auf dem 5% Niveau.

Hadinia et al., 2016 eingereicht

Rückmeldung: Anti-Stress Gruppentraining

- Gute Akzeptanz
- Belastungserleben
  - Emotionales Belastungserleben ↓
  - Somatisch motorisches Belastungserleben ↓
  - Kognitives Belastungserleben ↓
- Lebensqualität
  - Aktivität des täglichen Lebens ↑ (Trend)
  - Mobilität ↑ (Trend)
- Krankheitsbezogene Kommunikation

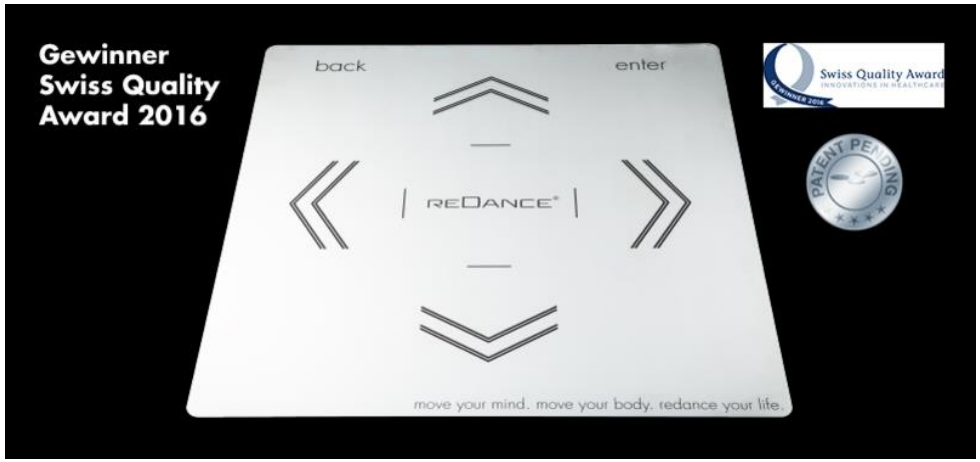
Sprachstudie

- Sprachtrainingsstudie nach Kaufman®
- Bei Patienten mit Parkinson Krankheit mit und ohne tiefe Hirnstimulation
- Voraussetzung: hochfrequente Teilnahme (Intensiv-Therapie)

Inhalt Sprachstudie

Studienablauf für Patienten mit Parkinson (mit und ohne tiefen Hirnstimulation)		
	Inhalt	**Dauer**
1. Woche	**1. Untersuchung:** – Sprachuntersuchung – Elektrophysiologische Untersuchung – Neuropsychologisch/psychiatrische Untersuchung	3h
2. Woche	**3 Therapie-Einheiten:** Sprachtherapie oder rBMT	Je ca. 30-45 Min.
3. Woche	**3 Therapie-Einheiten:** Sprachtherapie oder rBMT	Je ca. 30-45 Min.
4. Woche	**3 Therapie-Einheiten:** Sprachtherapie oder rBMT	Je ca. 30-45 Min.
5. Woche	**3 Therapie-Einheiten:** Sprachtherapie oder rBMT	Je ca. 30-45 Min.
6. Woche	**2. Untersuchung:** – Sprachuntersuchung – Elektrophysiologische Untersuchung – Neuropsychologisch/psychiatrische Untersuchung	3h
24. Woche	**3. Untersuchung:** – Sprachuntersuchung – Elektrophysiologische Untersuchung – Neuropsychologisch/psychiatrische Untersuchung	3h

Innovatives Tanzsystem (in Kooperation mit ETH zürich)



Quelle: http://www.redance.ch/page/wirkung/sturzpraevention.html (13.10.2016)

Erwarteter Nutzen

- Logopädie:
  - Aussprache
  - Sprachmelodie
  - Wortfindung
  - Sprachliche Flüssigkeit
- Tanzen
  - Training von Rhythmus und Beweglichkeit
  - Sturzprophylaxe
  - Allgemeine Steigerung des Wohlbefindens durch musikalische Stimulation
  - Video: http://www.redance.ch/page/produkt/tanzsystem.html

Herzlichen Dank!

Für weitere Informationen zum Sprachprojekt wenden Sie sich an:

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