Session Number: 5528

Behavior management and psychopharmacology in children with autistic spectrum disorders

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OCALI

November 17, 2011 - 4:30 - 5:45 pm

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Disclosures

- **Dr. Coplan is author of *Making Sense of Autistic Spectrum Disorders: Create the brightest future for your child with the best treatment options* (Bantam-Dell, 2010), and receives royalties on its sale**

- **This presentation will include a discussion of off-label drug use**

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"Behavior"

- **"The manner of conducting one's self"**
- **"Anything than an organism does involving action and response to stimulation"**
- **"The actions or reactions of a person or animal in response to internal or external stimuli"**

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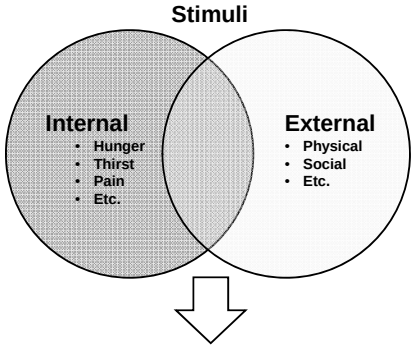

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"Internalizing" Behavior

- **Anxiety**
- **Depression**
- **Obsessiveness / Rigidity**
- **Perfectionism**

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"Externalizing" Behavior

- **Tantrums**
- **Property Destruction**
- **Aggression towards others**
- **Self-injurious behavior (SIB)**

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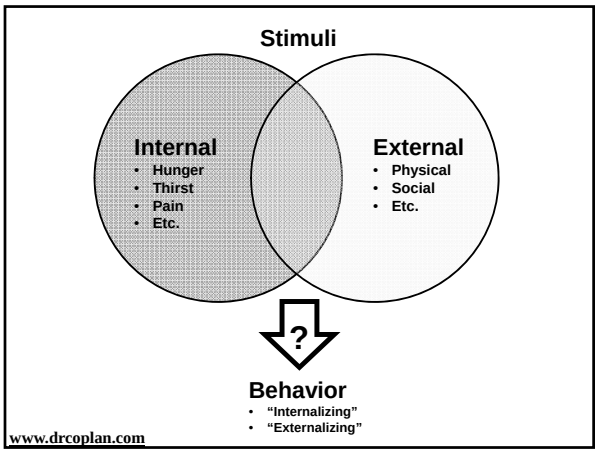


Behavior

- What is the child's developmental level?
- Is the behavior normal for the child's developmental level?
  - Tantrums / Noncompliance
  - "Impulsivity" / "Inattention"

Behavior

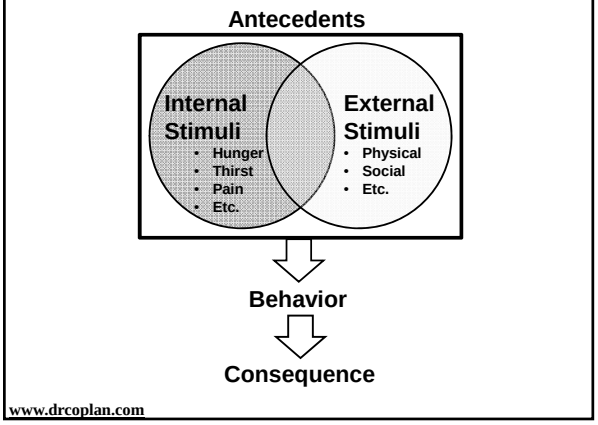
- What is the child's ability to communicate?
  - Does "disruptive" behavior serve a communicative function?

Behavior

- Acute change or chronic?
- General health?
  - Vital signs, I&O, Level of consciousness
  - Pain?
- Anything new in child's life?
  - Recent change of meds

The ABC's of Behavior Analysis

- What is the Antecedent?
- What is the Behavior?
- What is the Consequence?



Antecedents

- **External / Social:**
  - **Imposition of a task**
  - **Change in routine**
  - **Denial of access to object or activity**
  - **Other….**
  - **Or: No apparent external antecedent**

The ABC's of Behavior Analysis

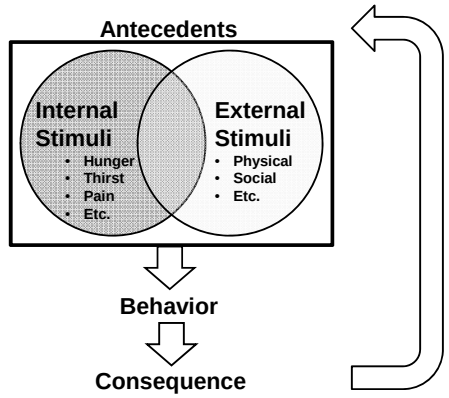
- **What is the Antecedent?**
- **What is the Behavior?**
- **What is the Consequence?**
  - **Reinforcers**
    - **Positive**
    - **Negative**
  - **Aversives**

Law of Effect

Animal Intelligence. EdwardThorndike, 1911

" Of several [possible] responses…to the same situation, those which are…closely followed by satisfaction to the animal will…be more likely to recur. Those which are…followed by discomfort to the animal will…be less likely to occur. The greater the satisfaction or discomfort, the great the strengthening or weakening of the bond"

Manipulating the Consequence for a given behavior feeds back on the probability that that behavior will recur.



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Consequences 1: Reinforcers

- **Reinforcers lead to an increase in frequency of the antecedent behavior**
  - **Positive Reinforcement (adds something)**
  - **Negative Reinforcement (removes something)**

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Positive Reinforcement

- **Attention (in neurotypical children)**
- **Access to desired object or activity**

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Negative Reinforcement

- **Escape (from a task, e.g.)**
- **Removal of an undesirable object (non-preferred food, e.g.)**
  - ***Negative reinforcement does not = "punishment"***

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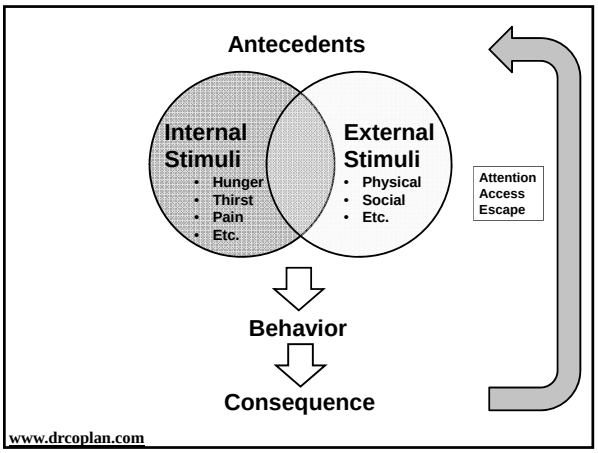

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Food Selectivity

Positive and Negative Reinforcement of unwanted behavior

- **Parent removes non-preferred food (negative reinforcement)**
- **Parent provides child with his/her preferred food (positive reinforcement)**
- **Alternatives**
  - ***First …..Then***
  - **Put refusal on extinction**
  - **The kitchen is *closed* between meals**
  - **Desensitization (non-preferred food is on table, on plate, touch, lick, mouth, eat)**

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Consequences 2: Aversives

- **Aversives lead to a *decrease* in the likelihood of recurrence of the antecedent behavior**
- **Logical Consequences**
  - **If child refuses to use toilet, child must carry backpack with spare clothes, when in public**
- **Over-correction**
  - **Must wash out soiled diaper (then discard)**
  - **If the child spills milk on purpose: child must mop the entire kitchen floor**

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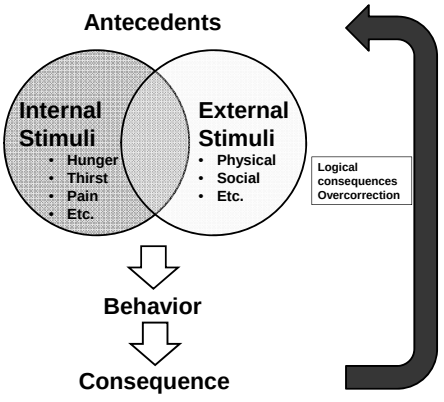

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Token Economy

- **Concretely specified behaviors**
- **Earn and Lose Points (Tokens)**
- **Points➡Access to specified reward**
  - **Reward determined by child's interests**
    - **Preferred toys**
    - **Computer time**
    - **Etc.**
  - **NO access to reward at other times**
  - **"Extra" treats not as effective**

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Token Economy

Camp David
Trading Post Rules

Rewards		Fees	
Good Day	+30	Bad Day	0
Doing Chore - Each	+10	Cursing - Each Time	-20
Doing a Good Deed	+10	Disrespect Parents	-10
Compliment About You	+10	Lies - Each	-20
Do Morning Work (NO Whining)	+10	Don't Do Morning Work (Whining)	-10
Do Pre-Bedtime Checklist	+5	Don't Do Pre-Bedtime Checklist	-5
		Ask More Than Once	-5
		Touch Another Kid or Being Mean	-10

Red = 5 White = 10 Blue = 50

Disruptive Behavior: Function & Best Response

- **Attention**
  - **1-2-3 ➡ "Time Out"**
- **Access**
  - ***Never* grant access to desired object in response to disruptive behavior**
- **Escape**
  - ***Never* permit the child to terminate a task with disruptive behavior. Walk child through task first, *then* ➡ Time Out.**

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But…..

Children with ASD have atypical responses to internal and external stimuli

- ***What good is Time Out if the child has no eye contact?***
- ***Obsessive behavior not the same as "ordinary" task refusal***

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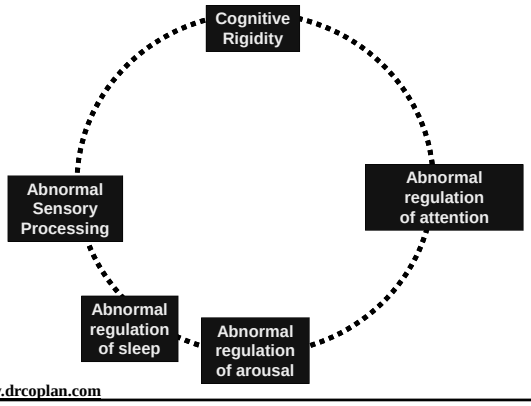
Neuropsychological Deficits in Persons with ASD



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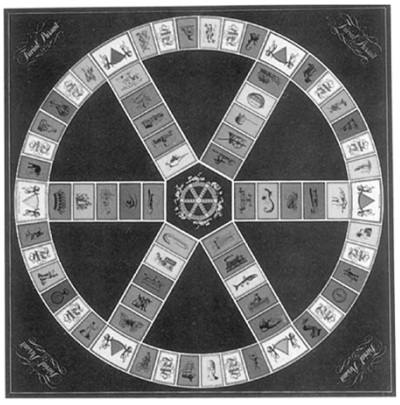

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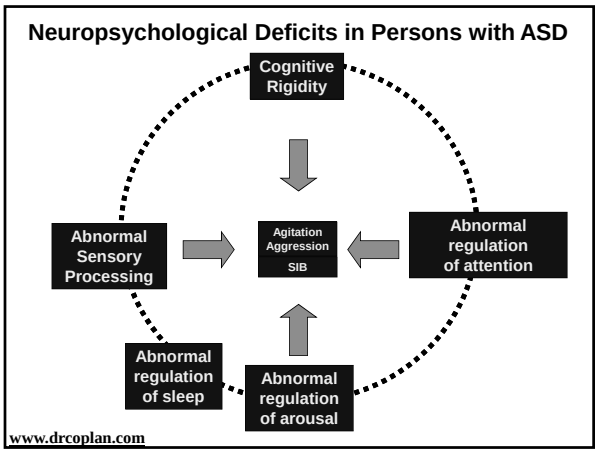
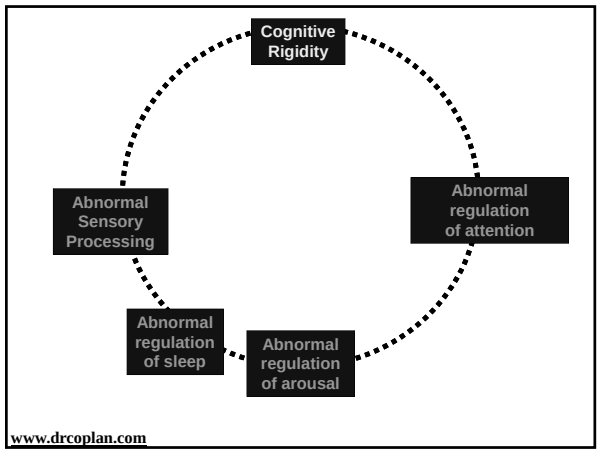
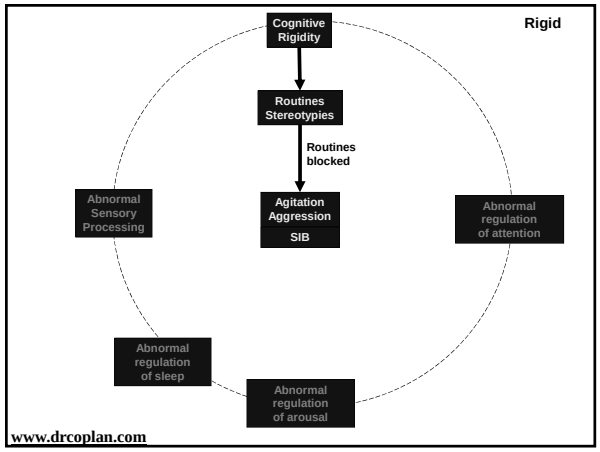




Cognitive Rigidity

- ***Insistently*** **repetitious behavior**
- **Problems with changes in routine, transitions, unmet expectations**
- **Perfectionism**
- **(Anxiety)**
- **(Depression)**



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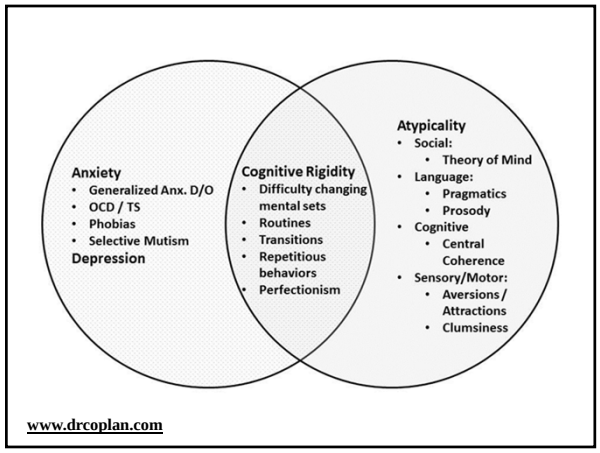
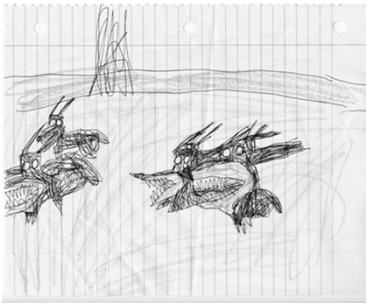


Anxiety



RD. 7 y.o. F, nl IQ, PDD-NOS & Anxiety. Fam Hx: GAD
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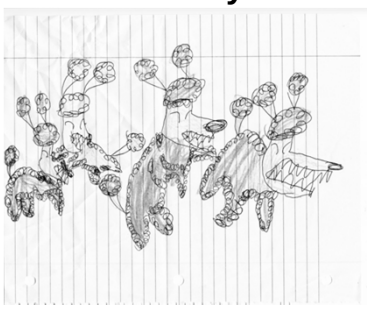
Anxiety



RD. 7 y.o. F, nl IQ, PDD-NOS & Anxiety. Fam Hx: GAD
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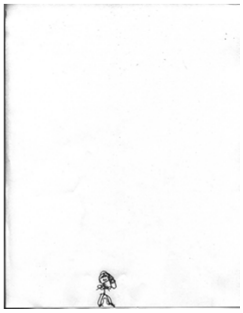
Depression



www.drcoplan.com KO; 10 yr old female, PDD-NOS, normal IQ

Cognitive Rigidity

- **Interventions**
  - **Visual Schedules**
    - **What am I supposed to be doing do *now*?**
    - **What am I supposed to do *next*?**
  - **CBT, Relaxation Techniques**
  - **SSRIs**

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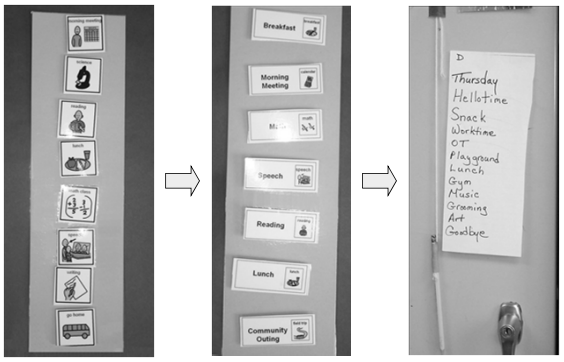

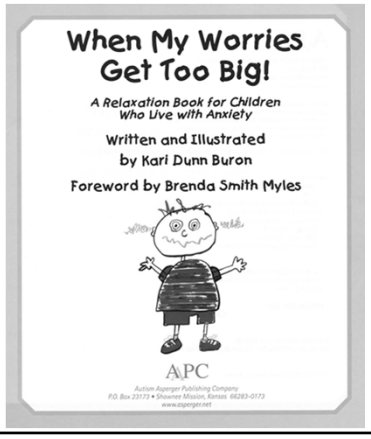

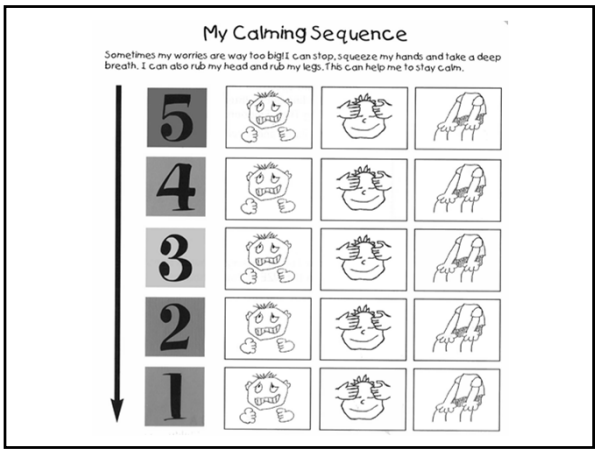

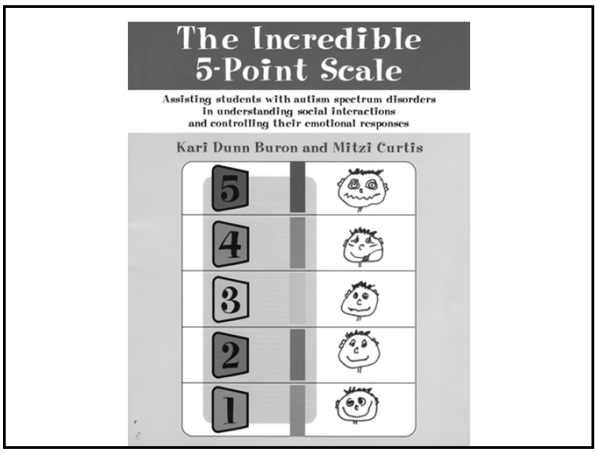

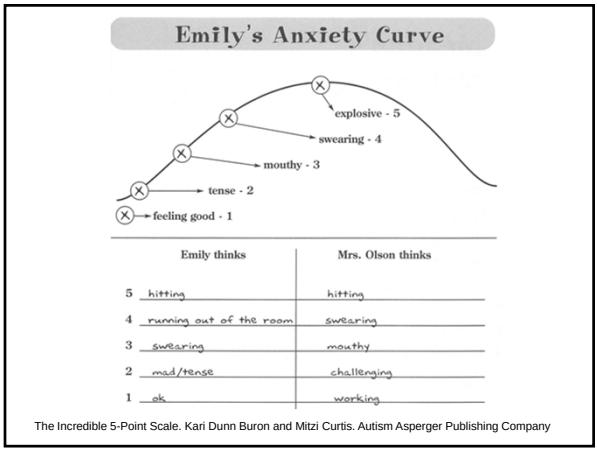

SSRIs in ASDs

- **Primary targets**
  - **Cognitive Rigidity**
    - **Anxiety**
    - **Obsessive / Perfectionistic behavior**
  - **Depression**
  - **? Stereotypies**
- **"Downstream" benefit:**
  - **↓ Disruptive Behavior**
  - **↑ Quality of Life**

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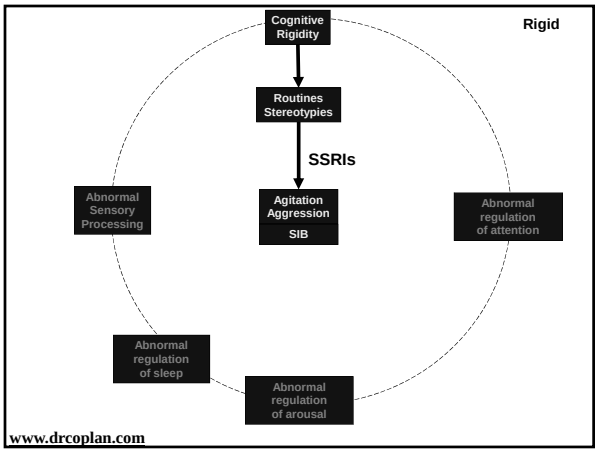
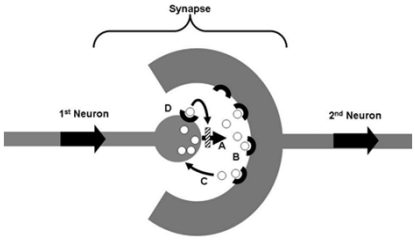
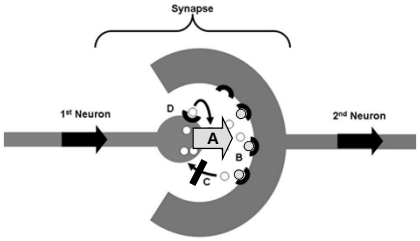


Neurotransmitters



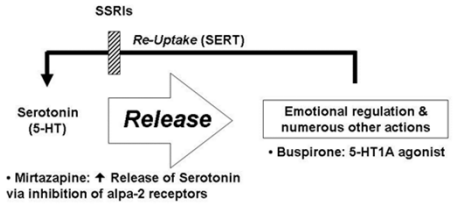
A: Release of transmitter by 1st neuron
B: Transmitter acts at receptor sites on 2nd neuron
C: Transmitter is taken up, and re-stored in 1st neuron
D: Autoreceptor on 1st neuron: detects release of transmitter

Serotonin promoting (serotoninergic) drugs



A. Promote release of serotonin (Mirtazipine)
B. Mimic the action of serotonin at the 2nd neuron (Buspirone)
C. Block re-uptake of serotonin (SSRIs)

Serotonin-promoting (serotoninergic) drugs



Selective Serotonin Reuptake Inhibitors block the re-uptake of Serotonin

Selective serotonin reuptake inhibitors (SSRIs) for autism spectrum disorder (ASD).

Williams, K., et al., Cochrane Database Syst Rev, 2010. 8: p. CD004677

- Studies reviewed: 7 randomized controlled trials / 271 participants
  - Fluoxetine (2), fluvoxamine (2), fenfluramine (2), citalopram (1)
  - Subjects: Children (5); Adults (2)
  - Varying inclusion criteria for Dx of ASD and IQ
  - 17 different outcome measures
- "Data were unsuitable for meta-analysis"

Selective serotonin reuptake inhibitors (SSRIs) for autism spectrum disorder (ASD).

Williams, K., et al., Cochrane Database Syst Rev, 2010. 8: p. CD004677

Authors' conclusion:

"There is no evidence that SSRIs are effective as a treatment for children with autism. In fact, there is emerging evidence that they are not effective and can cause harm. As such SSRIs cannot be recommended as a treatment for children with autism at this time."

Selective serotonin reuptake inhibitors (SSRIs) for autism spectrum disorder (ASD).

Williams, K., et al., Cochrane Database Syst Rev, 2010. 8: p. CD004677

- Treatment-emergent symptoms
  - Citalopram: 1 child with new onset seizures (continued to have seizures after citalopram was stopped)
  - Fenfluramine: ↑ stereotypies; withdrawal, sadness; ↓appetite
    - "With monitoring, dose adjustment and time, all but one of these adverse effects were resolved"
  - Fluoxetine (Hollander 2005): 6 of 37 children had their dosage reduced due to agitation
    - 2 children in the placebo group also had their "dosage" reduced. Difference between groups: Not significant
    - Reviewers disregard the fact that by the end of the trial, "anxiety and nervousness" was lower in the fluoxetine group compared to placebo: 15.9% vs. 33%.
  - Fluvoxamine: No significant difference in side effects between SSRI and placebo

Pharmacotherapy for anxiety disorders in children and adolescents

Ipser JC, Stein DJ, Hawkridge S, Hoppe L. Cochrane Database of Systematic Reviews 2009, Issue 3.

- Studies reviewed: 22 RCTs/ 2,519 participants
  - Short-term (average 11 wks)
  - Mean age 12 yrs
  - Drugs studied (versus placebo)
    - SSRIs :15 (fluoxetine 6, fluvoxamine 2, paroxetine 3, sertraline 4)
    - SNRIs: 5, (clomipramine 3), venlafaxine 2)
    - Benzodiazepines: 2: (alprazolam 1, clonazepam 1)
    - Tricyclic antidepressants: 1 (desipramine)
- Meta-analysis
  - Response rate: Medication 59%; Placebo 31%
  - 7.3% of subjects treated with SSRIs withdrew because of side effects
  - "The overwhelming majority of evidence of efficacy was for the SSRIs, with the most evidence in paediatric OCD"

Dimensional predictors of response to SRI pharmacotherapy in obsessive–compulsive disorder

Landeros-Weisenbergera et al. J. Affective Disord. v121, Issues 1-2, 2/2010, 175-179

OCD Subtypes:

- "Aggressive" Obsessions & Checking Behavior (AGG)
- Sexual / Religious (SR)
- Contamination & Washing (CW)
- Symmetry & Exactness (SYM)
- Hoarding (HRD)

Dimensional predictors of response to SRI pharmacotherapy in obsessive–compulsive disorder

Landeros-Weisenbergera et al. J. Affective Disord. v121, Issues 1-2, 2/2010, 175-179

Baseline demographical and clinical characteristics				
	Total	Clomipramine	Fluvoxamine	Fluoxetine
Number	165	62	79	24
Age	35.9 ± 11.0	35.1 ± 10.8	37.2 ± 11.7	34.0 ± 8.9
Gender	69 M	27 M	32 M	10 M

Dimensional predictors of response to SRI pharmacotherapy in obsessive–compulsive disorder

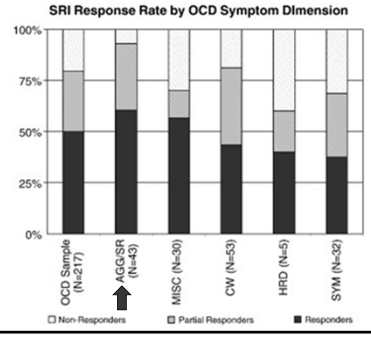
Landeros-Weisenbergera et al. J. Affective Disord. v121, Issues 1-2, 2/2010, 175-179

Result:

- Subjects with "aggressive obsessions" and checking behavior (and/or Sexual Religious obsessions) showed the best response to SRIs

Dimensional predictors of response to SRI pharmacotherapy in obsessive–compulsive disorder

Landeros-Weisenbergera et al. J. Affective Disord. v121, Issues 1-2, 2/2010, 175-179



A Placebo Controlled Crossover Trial of Liquid Fluoxetine on Repetitive Behaviors in Childhood and Adolescent Autism

Hollander, E, et al. Neuropsychopharmacology (2005) 30, 582–589

Subjects

- 45 subjects → 39 completers: 30 (77%) male, 9 (23%) female
- Age 5 - 16 years (mean 8 yr.)
- Mean IQ 64; range 30–132; MR: 23 (59%)

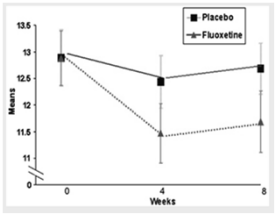
Protocol

- Fluox. or Placebo x 8 wk / 4 week "washout" / Fluox. or Placebo x 8 wk
- Mean dose 9.9 mg / d (+/- 4.4 mg)
- Children's Yale-Brown Obsessive-Compulsion Scale (CY-BOCS)
- Clinical Global Improvement Scale-Autistic Disorder (CGI-AD)
- Fluoxetine Side Effects Checklist (FSEC)

A Placebo Controlled Crossover Trial of Liquid Fluoxetine on Repetitive Behaviors in Childhood and Adolescent Autism

Hollander, E, et al. Neuropsychopharmacology (2005) 30, 582–589

Fluoxetine was superior to placebo in the treatment of repetitive behaviors by CY-BOCS (linear trend x treatment interaction z=-2.075, SE=0.407, p=0.038)



A Placebo Controlled Crossover Trial of Liquid Fluoxetine on Repetitive Behaviors in Childhood and Adolescent Autism
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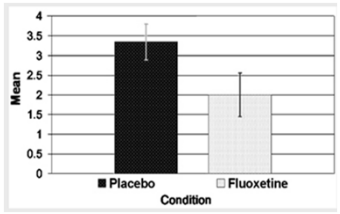
Fluoxetine was marginally superior to placebo on the improvement of the CGI change scores (z=-1.907, SE=0.703, p=0.056)



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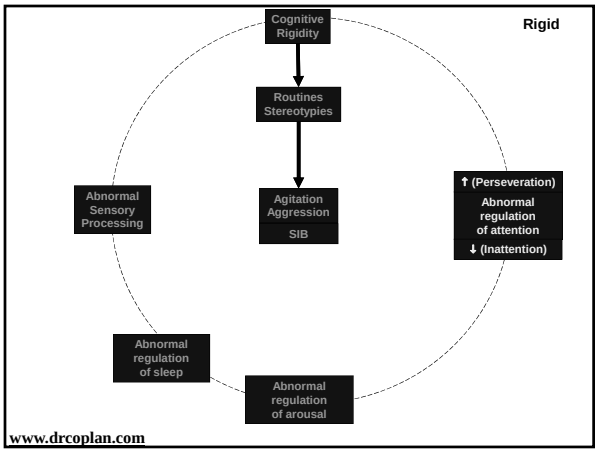
Fluoxetine did not significantly differ from placebo on treatment emergent side effects

Symptom	Fluoxetine	Placebo
Anxiety/nervousness	15.9% (6/39)	33.3% (12/36)
Insomnia	35.9% (14/39)	47.2% (17/36)
Drowsiness/fatigue/sedation	17.9% (7/39)	11.1% (4/36)
Agitation	46.2% (18/39)	44.4% (16/36)
Diarrhea	5.1% (2/39)	19.4% (7/36)
Anorexia	15.4% (6/39)	11.1% (4/36)
URI	10.3% (4/39)	19.4% (7/36)
Weight gain	0% (0/39)	2.8% (1/36)

A Placebo Controlled Crossover Trial of Liquid Fluoxetine on Repetitive Behaviors in Childhood and Adolescent Autism
Hollander, E, et al. Neuropsychopharmacology (2005) 30, 582–589

Conclusion

"Our results demonstrate that liquid fluoxetine reduced repetitive behaviors in children and adolescents with autism. We found a statistically significant reduction in repetitive behaviors, with a moderate to large effect size (0.76). "



Regulation of Attention

Shift

Attend to stimulus #1 ⟷ **Attend to stimulus #2**

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Abnormal Regulation of Attention - 1

- **Perseveration**
  - **Inability to "Let go and shift"**
  - **Gets "stuck"**
  - ***"Overattention Deficit Disorder"***
- **Compounds the effects of cognitive rigidity**

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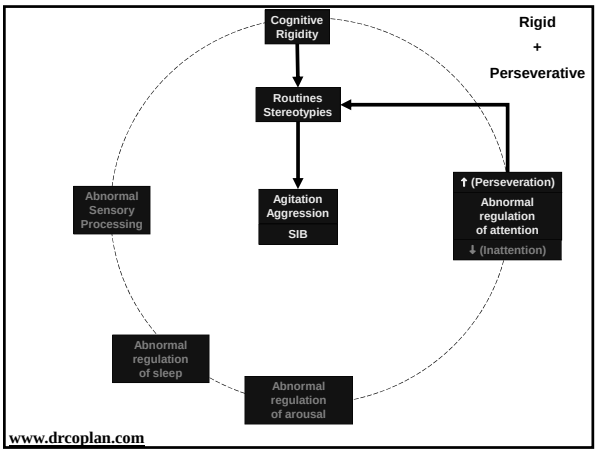

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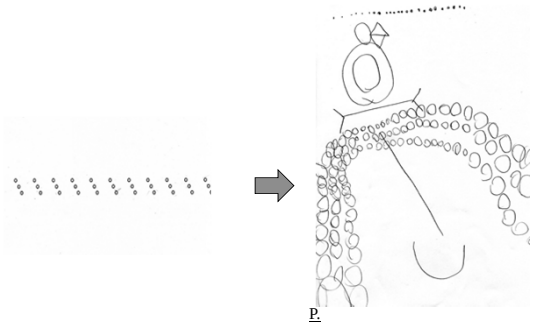
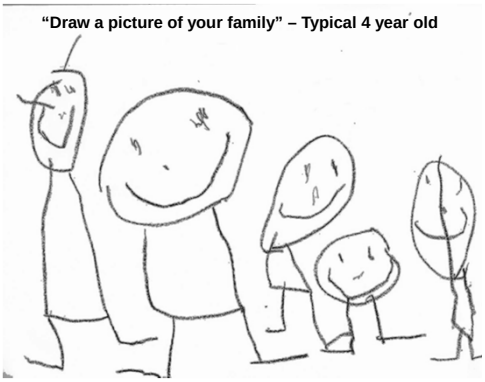
Perseveration



P.

"Draw a picture of your family" – Typical 4 year old



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"Draw a picture of your family" – 8 yr old with ASD

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Abnormal Regulation of Attention (Perseveration)

- **Interventions**
  - **Verbal preparation for transitions**
  - **Visual Schedules**
  - **SSRIs (OCD: Proven; ASD: likely)**

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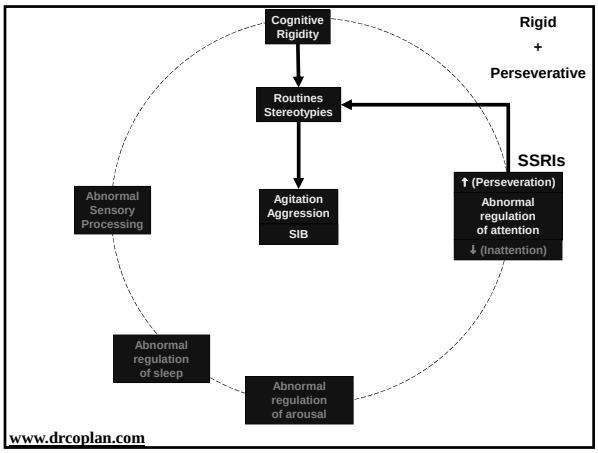

Abnormal Regulation of Attention - 2

- **Inattention**
  - **Inability to focus**
  - **Impulsive**
  - **Distractible**

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Inattention

- **Interventions**
  - **Limited stimuli**
  - **Short work periods**
  - **Medication**
    - **Stimulants, NRIs (may ↑ anxiety / rigidity / agitation)**
    - **alpha-2 agonists**

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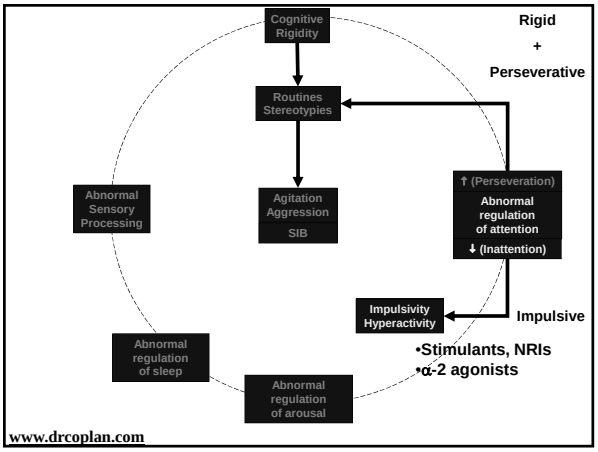
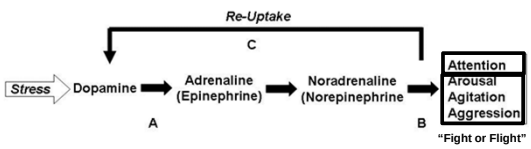


Stimulants, NRIs

(Dopaminergic; Sympathomimetic)



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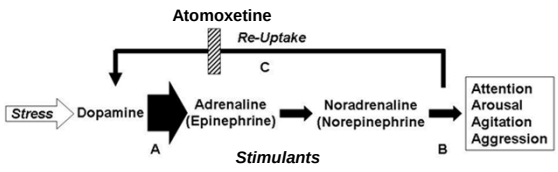
Dopaminergic Drugs



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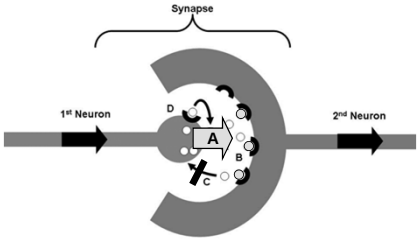
Dopamine promoting (dopaminergic) drugs



A. Promote release of Dopamine & Norepinephrine (Stimulants)
B. Mimic the action of Dopamine & Norepinephrine (Stimulants)
C. Block re-uptake of Dopamine & Norepinephrine (Atomoxetine)

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Stimulants, NRI's

Generic Name(s)	Brand Name(s)	Comment
Amphetamine		FDA Schedule II
Dextroamphetamine	Dexedrine, Dextrostat	FDA Schedule II
Dextroamphetamine + amphetamine	Adderall	FDA Schedule II
Methylphenidate	Concerta, Ritalin, Metadate	FDA Schedule II
Dexmethylphenidate	Focalin	FDA Schedule II
Atomoxetine, Attentin	Strattera	Norepinephrine reuptake Inhibitor (NRI), not FDA Schedule II

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References

(Stimulants)

Nickels, K., et al., Stimulant medication treatment of target behaviors in children with autism: a population-based study. J Dev Behav Pediatr, 2008. 29(2): p. 75-81.

Jahromi, L., et al., Positive Effects of Methylphenidate on Social Communication and Self-Regulation in Children with Pervasive Developmental Disorders and Hyperactivity. Journal of Autism and Developmental Disorders, 2009. 39(3): p. 395-404

Inattention

- **Beware of anxiety or perseveration masquerading as inattention**
  - **Perseveration on inner stimuli: "Inattentive"**
  - **Perfectionism: "Problems w. task completion"**
  - **Anxiety: "Rushes through work"**

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Alpha-2 Agonists

Generic Name	Brand Name(s)	Comment
Clonidine	Catapres	More sedating than guanfacine
Guanfacine	Tenex, Intuniv	

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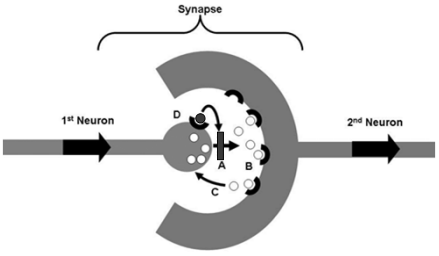
Alpha-2 Agonists



•Alpha-2 agonists (guanfacine, clonidine) stimulate autoreceptors on the 1st neuron, inhibiting release of dopamine & norepinephrine

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References
(alpha-2 agonists)

- Murray, M.J., Attention-deficit/Hyperactivity Disorder in the context of Autism spectrum disorders. Curr Psychiatry Rep, 2010. 12(5): p. 382-8.
- May, D.E. and C.J. Kratochvil, Attention-deficit hyperactivity disorder: recent advances in paediatric pharmacotherapy. Drugs, 2010. 70(1): p. 15-40.

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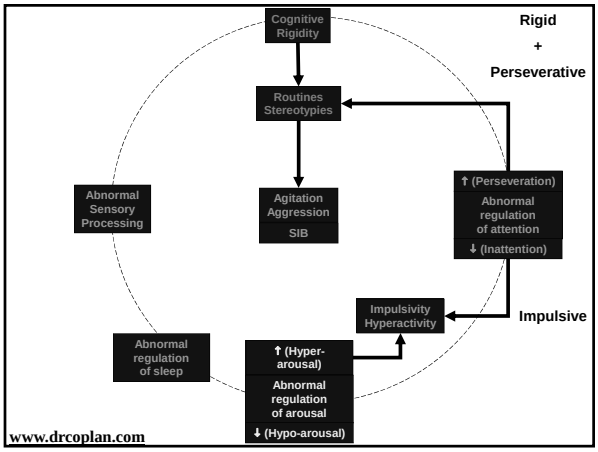

Regulation of Arousal

Hypoarousal
- Lethargic

Calm & Relaxed

Fight or Flight Response

"Red Alert"
⬆Adrenaline
⬆Heart Rate
⬆Resp. Rate
•Combative

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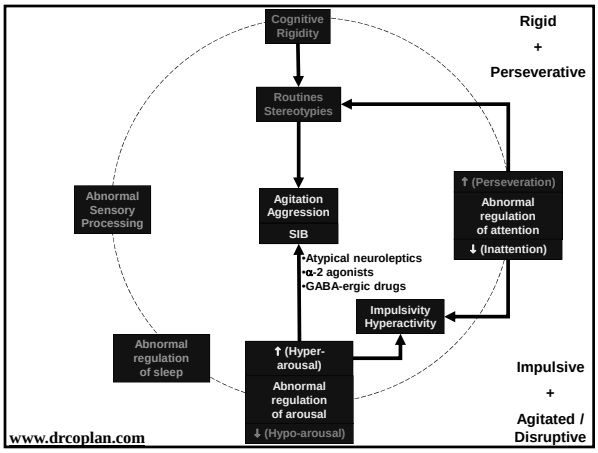
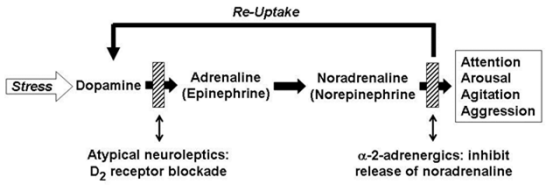


Dopamine antagonists



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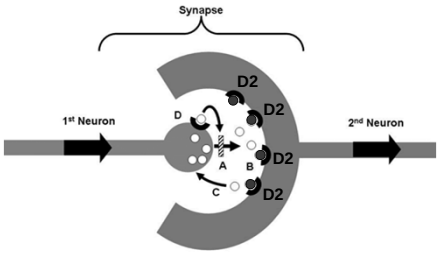
Atypical Neuroleptics



- Atypical neuroleptics block D2 receptors

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Atypical Neuroleptics

Generic Name	Brand Name	Comment
Aripiprazole	Abilify	Relatively less risk of weight gain
Clozapine	Clozaril	Causes bone marrow suppression
Olanzapine	Zyprexa	Greater risk of weight gain
Quetiapine	Seroquel	Greater sedation
Risperidone	Risperdal	• Greater risk of weight gain • Approved by FDA for treatment of agitation in children with ASD • Generic available
Ziprazidone	Geodon	Relatively less risk of weight gain

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References

(neuroleptics, AEDs, GABA)

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- Tuchman, R., AEDs and psychotropic drugs in children with autism and epilepsy. Mental Retardation & Developmental Disabilities Research Reviews, 2004. 10(2): p. 135-138.
- Wang, L.W., E. Berry-Kravis, and R.J. Hagerman, Fragile X: leading the way for targeted treatments in autism. Neurotherapeutics, 2010. 7(3): p. 264-74.

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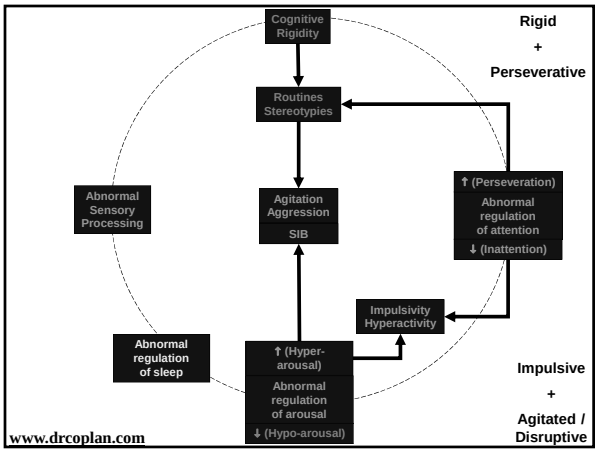

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Regulation of Sleep - 1

- **Melatonin**
  - Brain hormone
  - ↓ Metabolic rate (Heart, Temp)
  - "You're sleepy now"
- **Suppressed by light**
  - 24 hr cycle
  - Seasonal cycle

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Regulation of Sleep - 2

- **Abnormal melatonin cycling**
  - **Primary disorders of sleep**
  - **Blindness**
  - **ASD**
- **Symptoms**
  - **Delayed onset of sleep**
  - **Shortened duration / frequent wakening**

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Regulation of Sleep - 3

- **Shared genetic control**
  - **Regulation of sleep**
  - **Regulation of arousal**
- **Family history of sleep disorder**

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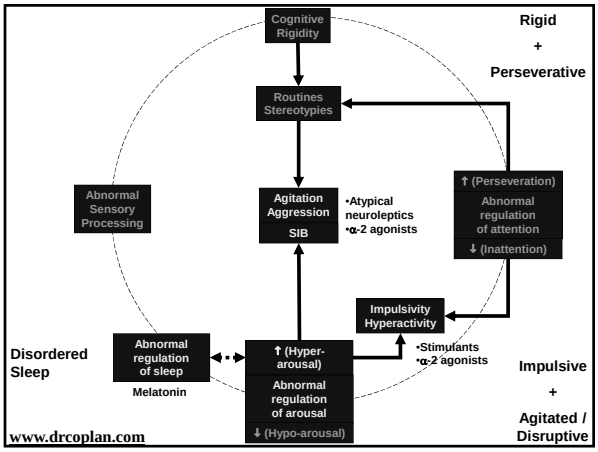

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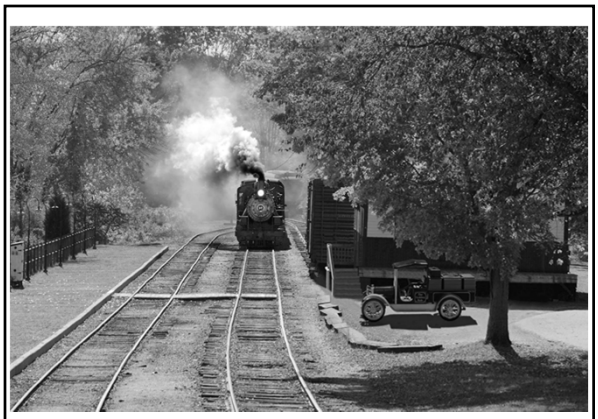
(Melatonin)

- Wright, B., et al., Melatonin Versus Placebo in Children with Autism Spectrum Conditions and Severe Sleep Problems Not Amenable to Behaviour Management Strategies: A Randomised Controlled Crossover Trial. J Autism Dev Disord, 2010.
- Miano, S. and R. Ferri, Epidemiology and management of insomnia in children with autistic spectrum disorders. Paediatr Drugs, 2010. 12(2): p. 75-84.
- Leu, R.M., et al., Relation of Melatonin to Sleep Architecture in Children with Autism. J Autism Dev Disord, 2010.



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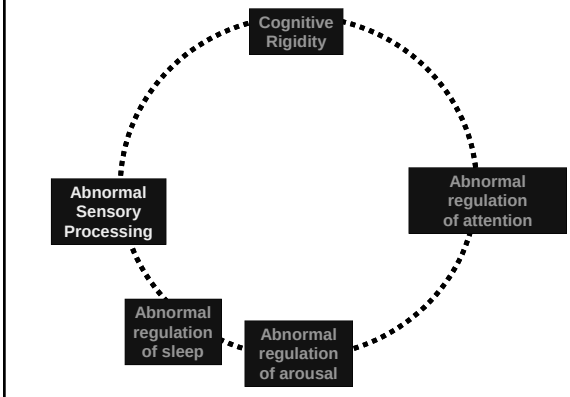

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Sensory Processing

- **Subjective Properties**
  - **Familiar / Unfamiliar**
  - **Pleasant / Unpleasant**
  - **Strong / Weak**
  - **Internal / External**
- **Sensory Input ➔ Self-awareness**
- **Mirror Neurons ➔ Empathy**

Mostofsky, S. and J. Ewen, *Altered Connectivity and Action Model Formation in Autism Is Autism*. Neuroscientist, 4/15/2011

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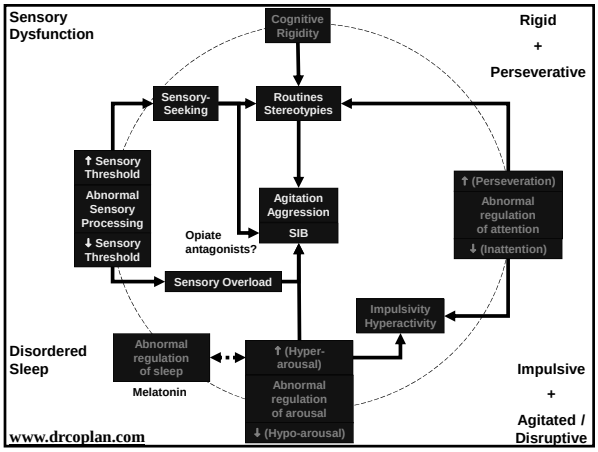

The whole is greater than the sum of its parts

Max Wertheimer

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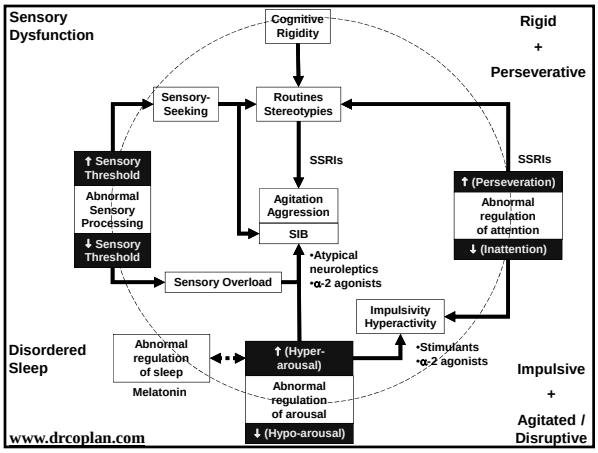

Summary

- **Why this child?**
  - **Extrinsic factors:**
    - **Functional behavioral assessment (Escape, access, attention)**
    - **Family assessment (Are mom & dad in synch?)**
  - **Intrinsic factors**
    - **Developmental Level (stage-appropriate behavior)**
    - **Cognitive Rigidity, Dysregulation of attention, arousal, sleep, or sensory processing**
- **Family & Behavioral Intervention – Usually**
- **Medication: Sometimes**

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Summary

Directions for future research:

- **Better phenotyping of ASD**
  - **Clinical**
  - **Genetic**
- **Better drug studies**
  - **Drug vs. Behavioral Therapy vs. Combination**
  - **Drug vs. Drug (not just drug vs. placebo)**
  - **Drug combinations (not just monotherapy)**
    - **Stimulant + SSRI, e.g.**
  - **Better outcome measures**
    - **Quality of Life**
    - **Long-term outcome**
- **Brain / Behavior / Drug imaging**

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Thank you

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