STAT 101B Research Project

Lecture 2

Drug and Non-Drug Treatments: Effects on Serotonin Levels

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ABSTRACT

Studies have shown that depression is the leading cause of disability in the United States, affecting millions of people every year. Medical professionals have linked low serotonin levels to depression. We have also found that running, massage, happy memories, MDMA, LSD, Dextroamphetamine are all linked to increasing serotonin levels. Thus, our study aims to determine which drug or alternative method is most effective at raising serotonin levels in the blood in order to help treat depression. The experimental design we chose was Latin Square in order to control for variability in participants and order of treatments. We sampled 24 participants from the northern part of the Island (women, ages 40-60) and used our subjects to perform our 6x6 Latin Square 4 times (6 participants per square). We randomized the order of the rows, columns, and order of treatments. To collect our data, we recorded blood serotonin levels beforehand, administered the treatment, waited the allotted amount of time for the given treatment, then recorded the blood serotonin level afterward. We waited 36 hours between administering the next treatment in order to ensure the previous treatment was void from the subjects' systems. Once we collected all our data, we created 5 linear models and created their respective ANOVA tables. These results showed that there is a significant relationship between treatment and change in blood serotonin levels. In fact, running in comparison to the other drug and non-drug treatments was the best at increasing blood serotonin levels and thus is the most effective at treating depression.

1. INTRODUCTION

According to the *National Institute of Mental Health*, depression is the leading cause of disability in the United States among people above the age of 18. By definition, depression is a

common, but serious mood disorder. It causes severe symptoms that affect how you feel, think, and handle daily activities, such as sleeping, eating, or working ("Depression"). This major mental health issue is affecting millions of people every year, so there has been research focused in this field of study. Although no two people are the same, there have been several studies focused on the best method of treatment for depression. Through this research, medical professionals have found a link between low levels of serotonin and depression (Young). Serotonin is an important chemical neurotransmitter in the human body that has a wide variety of functions. It is sometimes referred to as the "happy chemical" because it helps regulate mood, social behavior, appetite, digestion, sleep, memory, sexual desire, and function. In a neuroscience study focusing on the prefrontal cortical circuitry of the brain, it was confirmed that behavioral phenotype shifts as serotonin activity increases between none (depressed/aggressive not anxious) to low (anxious/depressed) to high (not depressed) (Albert).

As such an important neurochemical in the body, we were interested in how this chemical can be altered. Studies have shown that serotonin levels can be altered and affected by many different stimulants both natural and unnatural. Some of these altering stimulants include: food, sunlight, physical activity, meditation, relaxation techniques, happy memories, and other drugs that stimulate this chemical or release serotonin into the body. Treatment through the use of drugs has been the most common form that doctors use when helping a patient overcome any sort of disease or disorder. With this in mind, we wanted to include both forms of treatments (drug and non-drug) to ensure that we were truly finding the most effective form of treatment.

For this study we narrowed down our list of serotonin stimulants to three drug and three non-drug methods with the aim to find the best treatment to help this depression epidemic. This list of six treatments includes swedish massage, reflection of happy memorie, physical exercise through a 5 km run, 10 mg dosage of Dextroamphetamine, 50 mg dosage of Methylenedioxymethamohetamine (MDMA), and 100 μg dosage of Lysergic acid diethylamide (LSD). It is through these drug and alternative methods that we aim to find the best method of increasing serotonin levels in the blood in the pursuit to determine which treatment is best at treating depression.

2. METHODS AND PROCEDURES

2.1 Participants

The virtual participants that were chosen for this study came from the online resource known as the *Island*. Based on research from several medical data journals, it is clear that women between the ages of 40-60 are the largest demographic suffering from depression. For this reason, we decided to hone in on this demographic for our research since chemicals in the body differ greatly depending on gender and age. Since person to person variability is always very high, we chose to do a 6x6 Latin Square design for our study. In order to increase power as well as our error degrees of freedom, we repeated this 6x6 Latin Square four times. This resulted in our necessary sample size of 24 participants. These 24 participants were selected from the northern parts of the Island since the exposure to sunlight varies depending on region. Sunlight exposure impacts serotonin levels so we decided to hold this factor constant in this study. The process of obtaining these participants required us to go into different cities in the northern region of the island and request consent from participants of our necessary gender and age requirements.

2.2 Design

The Randomized Latin Square design is beneficial to block/control for two sources of variation. In this study, these two nuisance factors are person to person variability and order of treatment. By controlling for these two factors, it will allow detection of significant results for serotonin levels in the blood to be more likely.

We created a 6x6 Latin Square matrix with each treatment occurring once per row, and once per column. These drug and non-drug treatments (Happy Memories, Massage, Running, Dextroamphetamine, LSD, and MDMA) were each assigned a letter from A-F. A visualization of this can be seen below.

A	B	C	D	E	F
F	A	B	C	D	E
E	F	A	B	C	D
D	E	F	A	B	C
C	D	E	F	A	B
B	C	D	E	F	A

We then randomized our matrix by shuffling the rows and columns in R to create a completely randomized Latin Square. Since random selection was unattainable on the island, we used R to randomly assign each participant to a row in the square which indicated the treatment order for each participant. This created a single blinded experiment.

2.3 Material and Procedure

Our data collection process was long and very complex. This process had a very specific time frame and took place over the course of 18 days. We created our specific time frame through extensive research on each of our treatments. We needed to allot enough time in between the administration of the treatments to ensure that the treatments were independent. Through extensive research on each of our treatments, we came to the conclusion that the longest amount of time that our chosen drugs would stay in the body was 24 hours. In order to be certain that these drugs were out of the system, we decided to wait 36 hours between administration of the treatments.

The process of our data collection was quite complex. First, we measured the current serotonin levels in the blood using the "Blood Serotonin" Test on the *Island*. Then, we waited 15 minutes and administered one of the six treatments to each of our 24 participants. The specific treatment that a participant received indicated how much time we needed to wait before checking the resulting serotonin levels in the blood. For happy memories, research indicated that we should wait 10 minutes after a participant relives their happy memories to measure the maximum level of serotonin after that treatment (Ramierez). For running, research indicated to wait 30 minutes after the participant runs 5 km (Wilson). For the swedish massage, research indicated to wait 5-10 minutes (Tiffany Field). The drugs on the other hand, required a longer wait time. For Dextroamphetamine, MDMA, and LSD research indicated to wait 3 hours after ingestion to measure the drug when it is at its peak level in the body (Ward, McCann UD, Wise). After data was collected each day, it was input into an Excel spreadsheet for further analysis later. This process was repeated every 36 hours for 18 days straight. Each day, every treatment was administered to one of the six participants in each latin square.

2.4 Instruments

To conduct our study, we used virtual tasks and people on the Island (http://island.maths.uq.edu.au/index.php). We selected our participants from the Island to gather

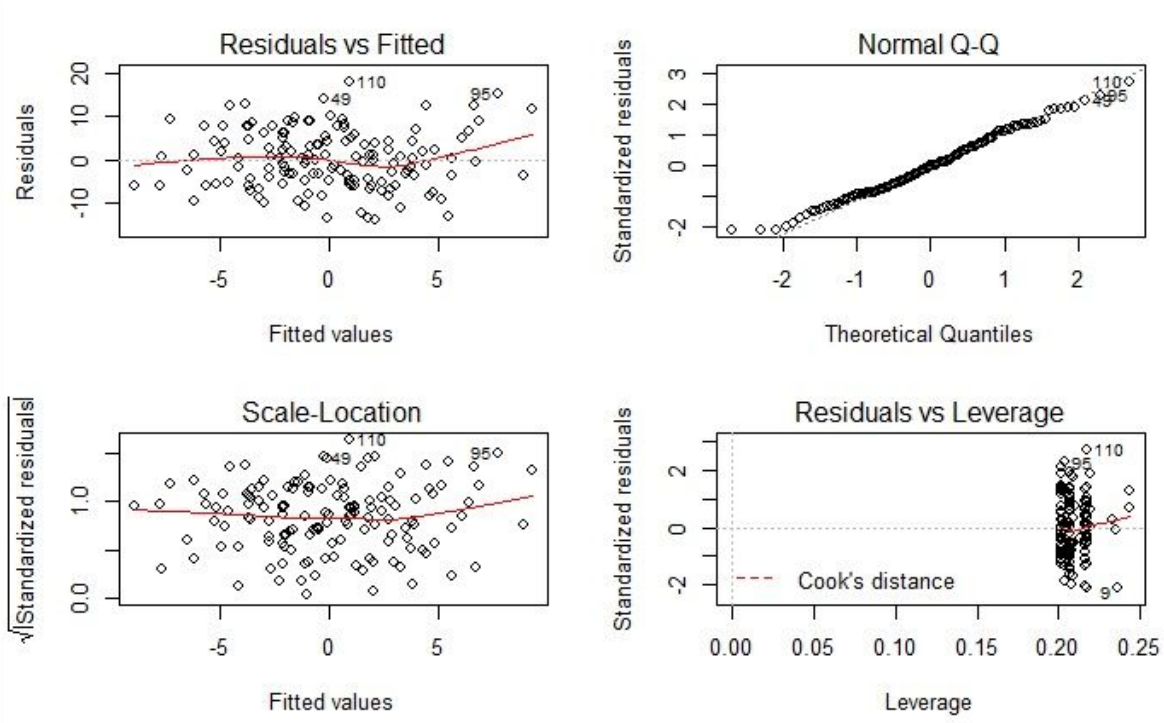
our sample. We also used available tasks on the Island to measure blood serotonin levels of our subjects (ng/mL) and administer our 6 treatments ("Swedish Massage," "Happy Memories," "Run Indoors 5 km," "Dextroamphetamine 10 mg," "Methylenedioxymethamphetamine 50 mg," and "Lysergic acid diethylamide 100 μg"). We used Microsoft Excel (https://products.office.com/en-US/excel?legRedir=true&CorrelationId=f8509c17-4263-4f13-a42d-62e6ca9f12fd) to record data collected on the Island. To conduct our analysis and create our models, we used base R and select packages in RStudio (https://www.rstudio.com/products/rstudio/download/). After completing our analysis in R, we used Tableau (https://www.tableau.com/products/desktop/download) to create visualizations.

2.5 Data Analysis

For the analysis we first loaded our data into R and used R to create models for each of our four Latin Squares and our combined data. We used the lm() function to achieve these models. We then used the plot() function to check the normality of residuals and constant variance assumptions to ensure our models were valid. Once we confirmed our models were valid, we did an analysis of variance breakdown for each of our 5 models using the aov() function to determine if our treatment predictor explained a significant amount of variation. This yielded degrees of freedom, sum of squares and mean sum of squares for row and column blocks and the treatment predictor, and their respective F and p-values. We then conducted some post-hoc analysis to determine specifically where certain variation in the treatment predictor was explained using both the boxplot() and TukeyHSD() functions to visually represent our findings. To create more aesthetic visualizations, we loaded our combined data into Tableau and created a boxplot.

3. RESULTS

3.1 Plots to Evaluate Validity of Models



Above are plots of the full model (combines all 4 Latin Squares). A bad leverage point was removed from the data in order to ensure that the assumptions for constant variance and normality of errors were met.

3.2 ANOVA tables

Latin Square 1

	Df	Sum Sq	Mean Sq	F value	Pr(>F)
Name	5	328.2	65.64	0.915	0.488
Day	1	34.3	34.29	0.478	0.496
Method	5	96.9	19.38	0.270	0.925
Residuals	24	1721.8	71.74		

Latin Square 2

	Df	Sum Sq	Mean Sq	F value	Pr(>F)
Name	5	432.5	86.49	1.275	0.3070
Day	1	5.3	5.26	0.078	0.7831
Method	5	1193.1	238.63	3.518	0.0158 *

Residuals	24	1628.1	67.84		

Latin Square 3

	Df	Sum Sq	Mean Sq	F value	Pr(>F)
Name	5	162.2	32.44	0.675	0.647
Day	1	0.3	0.34	0.007	0.933
Method	5	441.6	88.31	1.836	0.144
Residuals	24	1154.1	48.09		

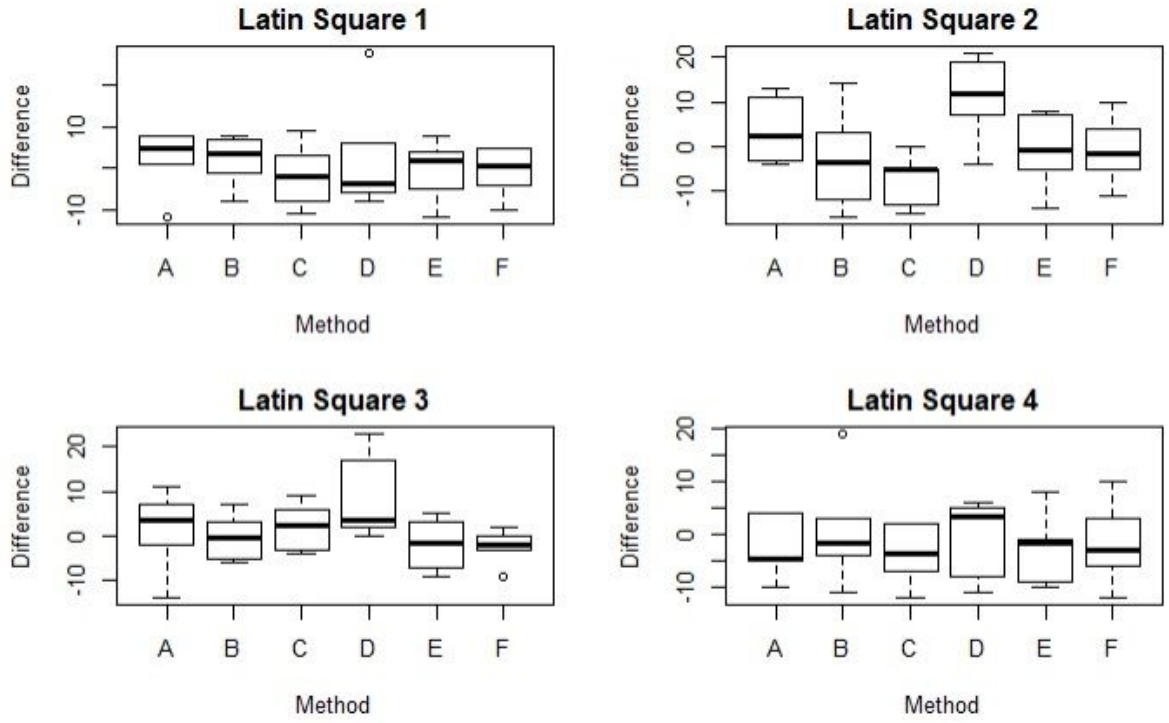
Latin Square 4

	Df	Sum Sq	Mean Sq	F value	Pr(>F)
Name	5	182.1	36.43	0.651	0.663
Day	1	69.8	69.78	1.247	0.275
Method	5	83.0	16.60	0.297	0.910
Residuals	24	1342.7	55.95		

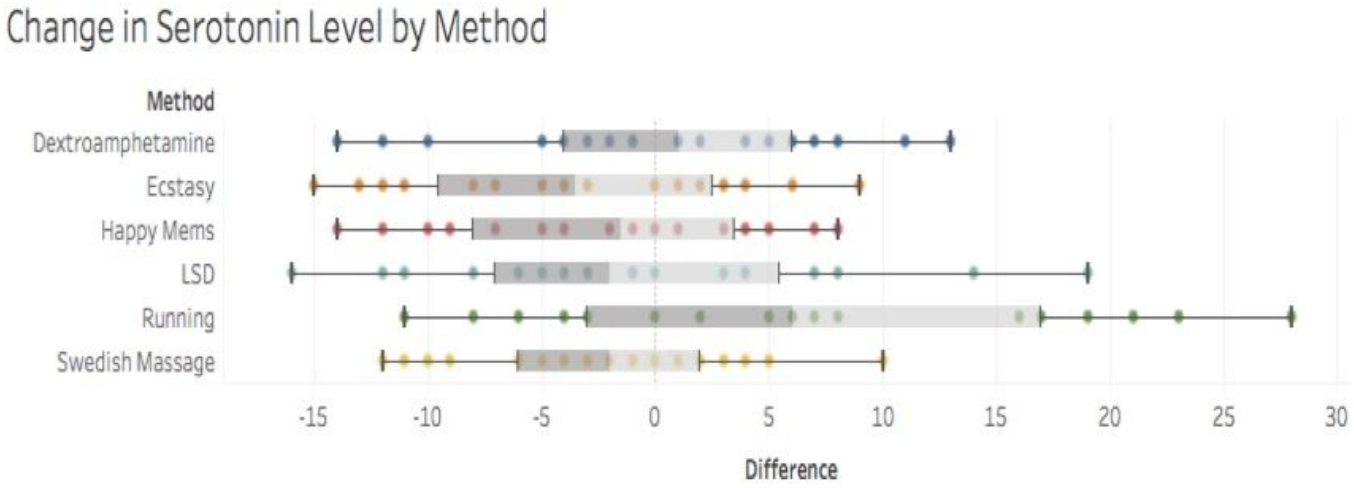
Combined Model (with removed bad leverage point)

	Df	Sum Sq	Mean Sq	F value	Pr(>F)
Name	23	1060	46.07	0.806	0.7176
Day	1	8	8.24	0.144	0.7049
Method	5	749	149.84	2.622	0.0278 *
Residuals	113	6459	57.16		

3.3 Graphs and Visualizations



Boxplots for all 4 Latin Squares (in R)



Boxplot of the Combined Data (in Tableau)

4. DISCUSSION

We first loaded the data for all 4 Latin Squares into R and created linear models for each of them. We checked the plots for them to ensure that the models were valid (constant variance and

normality of errors) before looking at the ANOVA tables. The ANOVA tables in the above section show that Method is not significant for Latin Squares 1, 3, and 4. The p-values of 0.925, 0.144, and 0.910 respectively are too high to satisfy our alpha value of 0.05. For these models we cannot conclude that there is a relationship between treatment method and change in blood serotonin levels. However, Latin Square 2 and the Combined Model show significant p-values for Method; the values are 0.0158 and 0.0278 respectively. We are particularly interested in the results for the combined model because it contains more values, which increases the power of our experiment. Thus, we can conclude for Latin Square 2 and the Combined Model that there is an association between treatment method and change in blood serotonin level.

We wanted to find out which treatment method explained most of the variation, so we created boxplots for each of our 5 models. As shown above, the combined data reveals that the running treatment displays the greatest change in blood serotonin levels. Thus, running a 5k indoors is the treatment that explains the statistical significance of our models.

It has been shown in past studies that exercise has been linked to lowering depression and increasing serotonin levels. Young's article explains that "the relation between exercise and mood concluded that antidepressant and anxiolytic effects have been clearly demonstrated" (Young). Exercise is linked to having certain antidepressant effects. Additionally, running for an extended period of time (>40 min) has scientifically shown to increase serotonin levels (Wilson). Our study and past scientific experiments have both affirmed that running is highly effective at increasing serotonin levels and curbing depression. Other studies have also shown that our other treatments (Swedish massage, happy memories, LSD, MDMA, and Dextroamphetamine) are also linked to increasing serotonin levels and decreasing depression's effects. However, our study has shown that running compared to the other treatments is most effective at achieving this pursuit. We reject our null hypothesis and conclude that there is a statistical difference in change in blood serotonin levels based on treatment method.

5. CONCLUSION

Depression is a serious mood disorder that causes severe symptoms that affect how you feel, think, and handle daily activities. Studies have shown that running, massages, recalling happy memories, LSD, MDMA, and Dextroamphetamine can raise serotonin levels in order to help treat depression. Through our research, we aimed to determine which of these drug and non-drug treatments is the most effective at raising blood serotonin levels.

Our results showed that there is a significant relationship between the treatments and raise in blood serotonin levels. Further analysis showed that running is the most effective treatment at raising blood serotonin levels. It is very common to treat depression these days with prescriptions for antidepressants. Our study showed that drug treatments for depression may not be the best solution. In fact, the non-drug treatment running had a larger impact in increasing serotonin levels compared to the other non-drug and drug treatments.

Although our experimental design is most suitable for the problem we are addressing, there are a few drawbacks to our design. The Latin Square design assumes no interaction between the row, column, and treatment factors. Although the effects of the administered drugs are technically out of the subjects' body after 36 hours, there still may be trace effects that may impact the performance of the next treatment. This means that there may be a supposed interaction between the column and treatment factors. Additionally, people are affected by stimuli in very different ways. Some of our subjects were not affected by the running treatment and had their largest increase in serotonin levels using a drug treatment. This may have occurred because some people do not like to run at all, so forcing them to run a 5k may not have a huge positive impact on their serotonin levels. Whereas, a certain drug treatment may work really well for a given subject in comparison. Another drawback of our design is that with a very extensive and complex data collection process, there is a higher chance for experimental error.

To improve our experiment in the future, we would like to repeat our experiment with more Latin Squares in order to get a larger sample size and increase power. We would also like to further control for the variability in subjects by administering a pre-screening survey to select participants from our sample with similar attitudes toward exercise, health, and drugs. Additionally, to decrease the amount of potential interaction between the column and treatment factors, we would increase the amount of time between administering treatments from 36 hours to 1 week. It would also be interesting to test different doses of the drugs and different amounts of time of the non-drug treatments to determine which level of each treatment is most effective at raising serotonin levels.

Notes:

Reasons to BLOCK

1. Reduce Background Noise (BN): Material is

naturally blocked (eg identical twins) so using this a part of the design may reduce BN

2. To protect against factors that may influence the experimental outcomes, and so cloud comparison of treatments

3. To assess block variation itself

eg day to day variation large may indicate a

Design and Statistical Analyses

The randomized block design is an extension of the paired t-test to situations where the factor of interest has more than two levels.

Read literature to know what factors and nuisance factors to consider

We assume

• treatments and blocks are initially fixed effects • blocks do not interact

Latin Square

- If you can block on two (perpendicular) sources of variation (rows x columns) you can reduce experimental error when compared to the RBD
- Randomize the order of the rows and randomize the order of the columns
- Each treatment occurs once in each block and once in each column
- More restrictive than the RBD
- Repeated Measures designs can remove order effects
- The total number of plots is the square of the number of treatments
- Each treatment appears once and only once in each row and column
- Advantage:
    - Allows the experimenter to control two sources of variation
    - This (in general) reduces MSE. This makes detection of significant results for the factor of interest more likely.
- Disadvantages:
    - The experiment becomes very large if the number of treatments is large
    - The statistical analysis is complicated by missing plots and misassigned treatments
    - Assumes no interaction among factors

- More complex than completely randomized design and randomized block design (but not too complex)
- Error df is small if there are only a few treatments
  - This limitation can be overcome by repeating a small Latin Square and then combining the experiments
    - a 3x3 Latin Square repeated 4 times
    - a 4x4 Latin Square repeated 2 times

Analysis

- Set up a two-way table and compute the row and column means and deviations □
- Compute a table of treatment means and deviations □
- Set up an ANOVA table divided into sources of variation
  - Rows
  - Columns
  - Treatments
  - Error
- Significance tests
  - F_T tests difference among treatment means
  - F_R and F_C test if row and column groupings are effective

II. Method

Response variable: Level of Serotonin in the blood

Predictors (treatments):

Drug: Dextroamphetamine, Lysergic acid diethylamide, Methylenedioxymethamphetamine

Non-Drug: Swedish massage, Run Indoors 5km, Happy Memories

Nuisance Factors: Person and Order

Problem: There is great person-to-person variability because every person reacts very differently.

Problem: Bodies may adapt to a drug or method. So even though a participant's bloodstream no longer has the drug, they might respond differently to the next treatment.

Coppen

- **SEROTONIN RELATIONSHIP TO DEPRESSION** Discusses research on the relationship between depression and serotonin (5-hydroxytryptamine [5-HT]). Animal studies show that the administration of tryptophan (the precursor of serotonin) increased serotonin synthesis and influenced behavior. Low plasma tryptophan levels have been found in patients with endogenous depression. Postmortem studies have shown an association between lowered hindbrain serotonin levels and suicide among depressed persons. The decreased serotonin levels in blood platelets during depression mirrored the neuronal changes. Tricyclic antidepressants inhibited platelet serotonin uptake and reduced imipramine binding sites on the platelets. A positive correlation between depression rating scores and platelet aggregatory response has been reported. Serotonin stimulated release of prolactin and growth hormone, although the prolactin response was less marked in depression.

"Depression."

- **DEPRESSION** Depression (major depressive disorder or clinical depression) is a common but serious mood disorder. It causes severe symptoms that affect how you feel, think, and handle daily activities, such as sleeping, eating, or working.
- Depression is one of the most common mental disorders in the U.S. Current research suggests that depression is caused by a combination of genetic, biological, environmental, and psychological factors.
- Quick Tip: No two people are affected the same way by depression and there is no "one-size-fits-all" for treatment. It may take some trial and error to find the treatment that works best for you.

Griffin, R. Morgan

- **EXERCISE** Exercise. It temporarily boosts feel-good chemicals called endorphins. It may also have long-term benefits for people with depression. Regular exercise seems to encourage the brain to rewire itself in positive ways, Cook says.
- **EXERCISE** How much exercise do you need? You don't need to run marathons to get a benefit. Just walking a few times a week can help.

Young

- **WHO IS AFFECTED BY DEPRESSION** The constitution of the WHO states "Health is a state of complete physical, mental and social well-being and not merely the absence of disease or infirmity."20 This may sound exaggerated but positive mood within the normal range is an important predictor of health and longevity. Several studies found an association between measures related to serotonin and mood in the normal range.
- **EXERCISE** As with exposure to bright light, there has been a large change in the level of vigorous physical exercise experienced since humans were hunter-gatherers or engaged primarily in agriculture.68 Lambert68 argued that the decline in vigorous physical exercise and, in particular, in effort-based rewards may contribute to the high level of depression in today's society. The effect of exercise on serotonin suggests that the exercise itself, not the rewards that stem from exercise, may be important. If trials of exercise to prevent depression are successful, then prevention of depression can be added to the numerous other benefits of exercise.
- **EXERCISE** A third strategy that may raise brain serotonin is exercise. A comprehensive review of the relation between exercise and mood concluded that antidepressant and anxiolytic effects have been clearly demonstrated
- **LIGHT** Exposure to bright light is a second possible approach to increasing serotonin without drugs. Bright light is, of course, a standard treatment for seasonal depression, but a few studies also suggest that it is an effective treatment for nonseasonal depression38 and also reduces depressed mood in women with premenstrual dysphoric disorder39 and in pregnant women suffering from depression

Wilson RUNNING AND SEROTONIN

- Extracellular hippocampal serotonin was higher ($p < 0.05$) during the first 40min of exercise than after 40min of being placed on the stationary treadmill, but this increase occurred only in those animals that learned more slowly and ran a shorter distance (1030+/-30m) and not in those that learned more rapidly and ran further (1150+/-20m).

Nishii EXERCISE DECREASES DEPRESSION

- These results suggest that long-term repeated exercise, regardless of the training intensity, improves depressive-like behavior through adaptive changes in the sensitivity of DRN and PVN neurons to acute exercise, and hippocampal neurogenesis.

Albert SEROTONIN DIRECTLY CORRELATED WITH DEPRESSION

- The model postulates that behavioral phenotype shifts as serotonin activity increases from none (depressed/aggressive not anxious) to low (anxious/depressed) to high (anxious, not depressed).

"LSD Alters Perception via Serotonin Receptors."

- **LSD** Researchers from the Department of Psychiatry, Psychotherapy and Psychosomatics at Zurich University Hospital for Psychiatry now reveal that LSD influences this process by stimulating the serotonin 2A receptor, one of the 14 serotonin receptors in the brain.
- **LSD** Researchers from UZH have discovered how the perception of meaning changes in the brain under the influence of LSD. The serotonin 2A receptors are responsible for altered perception. This finding will help develop new courses of pharmacotherapy for psychiatric disorders such as depression, addictions or phobias.

Garvey DEX REDUCES MANIA VIA SEROTONIN INCREASE

- Five of 6 acutely manic adult patients treated with dextroamphetamine experienced a 50% or greater reduction in their mania severity scores. Side effects were noted in only 1 S. Results suggest that dextroamphetamine might be useful in the treatment of mania through the enhancement of serotonin and acetylcholine.

Ward DEX TREATS DEPRESSION WELL, WAIT TIME

- Three hours after administration both drugs significantly improved depression and improved vigor, fatigue, and confusion-bewilderment on the subscales of the Profile of Mood States. Dex was significantly better than Fen only on the vigor and fatigue subscales. Other data from this study suggest that when used acutely Fen can mimic long-term antidepressant effects, whereas the acute effects of Dex are similar to its stimulating effects in normals.

Rudnick ECSTASY INCREASES SEROTONIN

- MDMA ("ecstasy") has been widely reported as a drug of abuse and as a neurotoxin. This report describes the mechanism of MDMA action at serotonin transporters from plasma membranes and secretory vesicles. MDMA stimulates serotonin efflux from both types of membrane vesicle.

Liechti ECSTASY PEAK SEROTONIN

- MDMA (1.5 mg/kg) predominantly produced an affective state of positive mood, moderate derealization, heightened sensory awareness, and a slight increase in psychomotor drive. The subjective effect of MDMA began 20 to 120 min after drug intake (mean 45 min), reached its peak 15 to 30 min later and lasted for a mean duration of 3 hours. After pretreatment with citalopram the effect of MDMA was markedly reduced but interestingly prolonged to a mean duration of 5 hours.

Piper ECSTASY DECREASES ANXIETY

- However, the MDMA group displayed an impairment of object recognition memory and reduced anxiety as indicated by a twofold increase in open-arm duration in the elevated plus-maze.

(not as good as Ramirez) Joormann HAPPY MEMS CAUSES BETTER MOOD

- Recent research suggests that the recall of positive memories plays an important role in mood regulation. In this study, the authors examined the ability of currently depressed, formerly depressed, and never-depressed participants to regulate sad mood through the recall of positive memories or through distraction. Although improvement in mood was found for all participants in response to distraction, under instructions to recall positive memories, never-depressed participants' moods improved, whereas formerly depressed participants' sad moods remained unchanged. It is important to note that depressed participants exhibited a worsening of their sad moods after recalling positive memories. These results suggest both that depression is associated with an impaired ability to use positive recall to regulate a sad mood and that this impairment continues to be evident following recovery. (PsycINFO Database Record (c) 2016 APA, all rights reserved)

RAMIREZ HAPPY MEMORIES SUPPRESSES DEPRESSION-LIKE BEHAVIOR

- Together, our data suggest that activating positive memories artificially is sufficient to suppress depression-like behaviours and point to dentate gyrus engram cells as potential therapeutic nodes for intervening with maladaptive behavioural states.

Tiffany Field MASSAGE HELPS DECREASE DEPRESSION

- Thirty-two depressed adolescent mothers received ten 30-minute sessions of massage therapy or relaxation therapy over a five-week period. Subjects were randomly assigned to each group. Although both groups reported lower anxiety following their first and last therapy sessions, only the massage therapy group showed behavioral and stress hormone changes including a decrease in anxious behavior, pulse, and salivary cortisol levels. A decrease in urine cortisol levels suggested lower stress following the five-week period for the massage therapy group.

"Cortisol decreases… SEROTONIN INCREASES FOLLOWING MASSAGE

- In this article the positive effects of massage therapy on biochemistry are reviewed including decreased levels of cortisol and increased levels of serotonin and dopamine. These studies combined suggest the stress-alleviating effects (decreased cortisol) and the activating effects (increased serotonin and dopamine) of massage therapy on a variety of medical conditions and stressful experiences.

"Can Massage Relieve Symptoms of Depression, Anxiety and Stress?"

- **MASSAGE** A 60-minute massage can lower cortisol, a hormone that's produced in response to stress, by an average of 30 percent. And when cortisol levels decline, serotonin — one of the body's anti-pain mechanisms — increases by an average of 28 percent after receiving a massage. By lowering cortisol and increasing serotonin, you're boosting your body's ability to fight off pain, anxiety and feelings of sadness.
- **MASSAGE** These studies have shown that massage reduces depression and anxiety and leads to a decrease in the levels of stress hormones in the bodies of participants.

Ricaurte, George A.,

- **ECSTASY** The popular recreational drug, (±)3,4-methylenedioxymethamphetamine (MDMA; 'Ecstasy') is a potent and selective brain serotonin (5-HT) neurotoxin in animals.

MDMA-induced 5-HT neurotoxicity can be demonstrated using a variety of neurochemical, neuroanatomical and, more recently, functional measures of 5-HT neurons.

McCann UD,

- **ECSTASY** The nerve pathway that is predominantly affected by ecstasy is called the serotonin pathway. Serotonin is a neurotransmitter that is synthesized, stored, and released by specific neurons in this pathway. It is involved in the regulation of several processes within the brain, including mood, emotions, aggression, sleep, appetite, anxiety, memory, and perceptions. a chemical like serotonin can regulate these processes.

Bengel, Dietmar,

- **ECSTASY** MDMA affects the brain by increasing the activity of at least three neurotransmitters (the chemical messengers of brain cells): serotonin,89,90dopamine, and norepinephrine.91 Like other amphetamines, MDMA enhances release of these neurotransmitters89–92and/or blocks their reuptake,93,94 resulting in increased neurotransmitter levels within the synaptic cleft (the space between the neurons at a synapse).
- **ECSTASY** MDMA causes greater release of serotonin and norepinephrine than of dopamine.91 Serotonin is a neurotransmitter that plays an important role in the regulation of mood, sleep, pain, appetite, and other behaviors. The excess release of serotonin by MDMA likely causes the mood-elevating effects people experience.

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