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Catechol-O-Methyltransferase gene Val158Met polymorphism as a potential predictor of response to computer-assisted delivery of cognitive-behavioral therapy among cocaine-dependent individuals: Preliminary findings from a randomized controlled trial

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Abstract

Background—Findings from uncontrolled studies suggest that the *COMT* Val108/158Met polymorphism may affect response to cognitive behavioral therapy (CBT) in some populations. Using data from a randomized controlled trial evaluating computerized CBT (CBT4CBT), we evaluated treatment response by *COMT* genotype, with the *a priori* hypothesis that Val carriers would have improved response to computerized delivery of CBT.

Methods—101 cocaine-dependent individuals, of whom 81 contributed analyzable genetic samples, were randomized to standard methadone maintenance treatment plus CBT4CBT or standard treatment alone in an 8-week trial.

Results—There was a significant genotype by time effect on frequency of cocaine use from baseline to the end of the 6-month follow-up, suggesting greater reductions over time for Val carriers relative to individuals with the Met/Met genotype. There was a significant treatment condition by genotype interactions for rates of participants attaining 21 or more days of continuous abstinence as well as self-reported percent days of abstinence, suggesting less cocaine use among Val carriers when assigned to CBT compared to standard treatment. Exploration of possible mechanisms using measures of attentional biased also pointed to greater change over time in these measures among the Val carriers assigned to CBT.

Conclusion—These are the first data from a randomized controlled trial indicating significant interactions of *COMT* polymorphism and behavioral therapy condition on treatment outcome, where Val carriers appeared to respond particularly well to computerized CBT. These preliminary data point to a potential biomarker of response to CBT linked to its putative mechanism of action, enhanced cognitive control.

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Disclosure

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Introduction

Biological markers of CBT response

Cognitive behavioral therapy (CBT) is an effective behavioral intervention for drug and alcohol use disorders and its putative active ingredients include learning of skills and strategies for regulating affect, changing maladaptive thoughts, and learning new behavioral strategies (1, 2). Neuroimaging findings suggest that CBT may induce plastic changes in the brain (3–7), underscoring that behavioral treatments can have biological effects (8), and that their moderators and mediators may be understood in terms of biological markers and neural processes.

CBT may represent a particularly promising candidate for evaluation of potential biologic markers of treatment response for several reasons: First, CBT has been demonstrated to be effective across a range of mental disorders, suggesting that it may target basic cognitive processes underlying multiple psychiatric disorders (9–11). Second, the relative durability of CBT's effects (12–14) underscore its links with learning and lasting changes in key cognitive and behavioral processes. Third, emerging evidence suggests CBT interventions address key elements of self-regulation and cognitive control (5, 14–16) as such, response to CBT may be linked to biological processes associated with executive functioning (7, 17–19).

More broadly, emphasis on behavioral and biological processes has begun to yield preliminary findings regarding genotypes as potential predictors of response to CBT and other empirically validated behavioral therapies. Efforts toward identifying genotypes that are associated with response to specific treatments hold the potential of fostering matches of patients with treatment to which they are more likely to respond (8, 20), as well as furthering our understanding of the mechanisms of successful behavior change.

COMT and cognition

Individual differences in executive cognitive function are strongly influenced by genetic variations (21, 22), raising the possibility that genetic variation may also contribute to individual differences in clinical response to CBT. One of the more promising genetic variations in this regard is a single nucleotide polymorphism (SNP) at codon 158 (Val158Met or rs4680) that results in the presence of methionine (Met) or valine (Val) in the membrane-bound catechol-O-methyltransferase (*COMT*) enzyme. *COMT* is the main enzyme that inactivates dopamine (DA) in the prefrontal cortical cortex (PFC). The enzyme with the Val allele is three to four times more active than that with the Met allele, resulting in reduced tonic DA levels combined with increased phasic DA release (23). Because of the sparse distribution of dopamine transporter in the PFC, functional impact of *COMT* activity is most pronounced in this region (24). While individuals with Met allele tend to be more efficient on cognitive tasks that require cognitive stability, Val carriers appear more efficient on tasks that require cognitive flexibility (i.e., adaptation to changing rules) (23, 25–27) (28, 29).

Preliminary studies have linked *COMT* Val158Met polymorphism to response to CBT in areas outside the addictions. In a sample of 69 individuals with panic disorder, Val carriers

appeared to respond better to exposure-based CBT than those with the Met/Met genotype (30), although the lack of a control condition and variable levels of concurrent pharmacotherapy across participants complicated interpretation of effects related specifically to CBT versus those attributable to other aspects of treatment. However, as the field of genetic predictors of response to behavioral therapies is still novel (31), it has been difficult to interpret mixed or inconsistent results across these early studies (32–37). To date, issues such as lack of control or comparison conditions, non-random assignment, heterogeneity in treatment delivery and widely varying outcome measures have precluded attribution of apparent genotype-related responsivity to CBT itself, as opposed to more general changes that might be associated with common effects of treatment or reductions in symptomatology over time.

COMT as a predictor of response to computerized CBT

Computer-assisted delivery of validated behavioral therapies represents a major step forward in broader dissemination and enhanced availability of evidence-based treatments (38, 39). In addition to dissemination, another key feature of computerized behavioral therapies is that they can be implemented at a comparatively high level of consistency and standardization. Standardization and reduction in ‘noise’ variability may in turn facilitate clearer understanding of salient determinants of treatment response and outcome, including genetic variation.

The efficacy and durability of one form of computerized CBT (CBT4CBT; Carroll et al., 2008) was recently replicated in a sample of cocaine dependent methadone-maintained individuals (40–42). As this project was supported through a NIDA MERIT award, the renewal application permitted testing of *COMT* polymorphism *a priori* as a potential predictor of response to CBT4CBT. We hypothesized that individuals carrying a Val allele would respond comparatively well to CBT4CBT with respect to standard treatment, given CBT’s emphasis on teaching strategies for enhancing cognitive control and flexibility. Moreover, because this trial evaluated an addicted population, we hypothesized that *COMT* genotype would also be associated with cocaine use outcomes, given that Val108/158 Met polymorphism has been associated with increased risk for addiction (43), including cocaine use disorders (44, 45) and linked to poorer treatment response in some samples. Based on data from general psychiatric (43) and addicted populations (46), we anticipated better overall response for Val carriers compared with those with the Met/Met genotype. Finally, as exploratory proof-of concept evaluation of possible cognitive correlates of *COMT* interactions with treatment type, we evaluated cognitive measures relevant to potential mechanisms of *COMT* polymorphism effects on differential response to CBT. Thus, we explored genotype-by-treatment interactions over time on a measure of attentional bias, the modified Stroop (47), comparing reaction times for cocaine-related versus neutral words.

Methods

Overview of study and participants

As described in greater detail in the main study report (42), patients were English-speaking adults, stabilized on methadone (no dose change >2 months), who met DSM-IV criteria for

current cocaine dependence. Exclusion criteria were minimal to facilitate recruitment of a broad and clinically representative group of individuals enrolled in this setting. Thus, individuals were excluded only if (1) they failed to meet DSM-IV criteria for current cocaine dependence, (2) had an unstabilized psychotic disorder or had current suicidal/homicidal ideation such that more intensive treatment was indicated, or (3) could not read at a 6th grade level. Following description of the study and provision of written informed consent approved by the Yale University School of Medicine Human Investigations Committee, participants were randomized to either standard methadone maintenance or standard methadone maintenance plus CBT4CBT, using a computerized urn randomization program (48) to balance treatment groups with respect to gender, ethnicity, education level, and baseline frequency of cocaine use.

Treatments

All participants were offered standard treatment at the clinic, which consisted of daily methadone maintenance and weekly group sessions. Participants also met twice weekly with a research assistant who collected urine specimens, assessed recent substance use and monitored other clinical symptoms. Those randomized to the CBT4CBT condition were provided access to the program on a dedicated computer in a private room within the clinic. The research assistant guided participants through their initial use of the CBT4CBT program and was available if needed to answer questions and assist participants each time they accessed the program. Participants accessed the program through an ID/password system to protect confidentiality. As described earlier (40), the CBT4CBT program was user-friendly and required no previous experience with computers nor reading skills (any material presented in text was also read by an on-screen narrator) and collects no PHI. The program was media-rich, using games, cartoons, quizzes and other interactive exercises to teach and model effective use of skills and strategies.

Assessments

Participants were assessed before treatment, twice weekly during treatment, at the 8-week treatment termination point, and 1, 3, and 6 months after the termination point by a research assistant. Participants were administered the Structured Clinical Interview for DSM-IV (SCID) (49) prior to randomization to establish substance use and other psychiatric diagnoses. The Substance Use Calendar, similar to the Timeline Follow Back (50), was administered weekly during treatment to collect day-by-day self-reports of drug and alcohol use for the 28-day period prior to randomization, as well as throughout the 56-day treatment phase and the 6-month follow-up. Participant self-reports of drug use were verified through urine toxicology screens that were obtained at every assessment visit; these were consistent with participant self-report in 88% of urine specimens collected (42). The modified Stroop task, a variation of the classic Stroop used to assess attentional bias to cocaine-related cues in multiple studies (51, 52) was added to the assessment battery after the trial began.. As shown in the CONSORT diagram (Figure 1), which presents data availability by treatment condition, of the 101 individuals who were eligible for the study, provided written informed consent and were randomized, 81 provided saliva samples from which DNA was extracted. Of these, 99% completed posttreatment assessment and 98% completed follow-up interviews six months after treatment ended.

DNA extraction and genotyping

Eighty-one participants gave written consent and provided samples for DNA testing. DNA was extracted from saliva samples using a commercial kit (PureGene™; Gentra, Minneapolis, MN). We used the TaqMan method and primers (supplied as pre-validated SNP Assays on Demand, Applied Biosystems) to genotype COMT Val 108/158Met (rs4680). The genotyping was performed using ABI PRISM 7900 Sequence Detection System (Applied Biosystems). All samples were genotyped in duplicate.

Data analyses

The *a priori* indicator of positive response was attainment of three or more weeks of continuous abstinence, a variable found in multiple trials to be predictive of better long-term cocaine outcomes (53, 54). Continuous primary outcome measures for the trial were self-reported drug use and results of results of urine toxicology screens (operationalized as the percentage of drug-negative urine samples collected during treatment). The principal data analytic strategy was random effects regression analysis for the longitudinal outcome (days of cocaine use by month through the treatment and follow-up periods) and analysis of variance for the other primary outcome variables (percent of urine specimens negative for cocaine; self-reported abstinence) with genotype and treatment condition as factors.

Results

Sample description

As shown in Figure 1, genotyping classified 17 participants (21%) as Met/Met; 35 (43%) as Met/Val, and 29 (36%) as Val/Val. This distribution satisfied the Hardy-Weinberg equilibrium (all chi-squares non-significant; overall $X^2=.23$, for Caucasian Americans $X^2=1.78$, for African Americans $X^2=0$). Consistent with previous work (25, 30, 32), the Met/Val and Val/Val groups were combined for all analyses. Table 1 presents baseline demographic characteristics and substance use and psychiatric diagnoses of the 81 participants by genotype. The majority were female (64%), European American (61.7%, African American 28.4%, Hispanic 8.6%), and most had completed high school (71.6%). The majority (80.2%) received some public assistance and 16% were on probation or parole. Participants reported that they used cocaine an average of 14.5 days a month and had been using for approximately 12 years. ANOVA and chi-square analyses indicated no significant differences by genotype on these and other baseline variables. Characteristics of the subgroup who provided genetic data did not differ from the full sample or those who did not agree to provide a saliva sample. (42).

Relationship of COMT genotype and overall treatment outcome

There were no significant differences by genotype for retention in treatment, number of urine samples provided or other indicators of data availability. Moreover, there were no main effects of *COMT* genotype on any of the primary within-treatment cocaine outcome measures. However, longitudinal analysis of frequency of cocaine use from baseline through the 6-month follow-up indicated a significant overall reduction in cocaine use over time (effect of month, $F(df\ 1,235)=80.8$, $p<.001$) as well as a significant genotype by time

interaction $F(df\ 1,235)=4.0, p=.047$), indicating greater reduction in frequency of cocaine use over time for individuals carrying the Val allele relative to individuals who were homozygous for the Met allele.

Treatment condition by genotype interactions

Primary outcomes are presented in Table 2 by genotype and treatment condition. There were significant genotype-by-treatment interaction on rates of participants attaining three or more weeks of consecutive abstinence within treatment, as well as self-reported days of abstinence, suggesting less cocaine use within treatment for individuals carrying a Val allele when assigned to CBT4CBT versus standard methadone maintenance, and somewhat better outcomes for those with the Met/Met genotype when assigned to standard treatment versus CBT4CBT. This is illustrated in Figure 2, which shows proportions of participants who attained three or more weeks of consecutive abstinence during treatment, a comparatively strong and consistent indicator of better long term outcomes (53, 54). These effects were largely accounted for by differences within the Val allele carriers ($X^2=3.6, p=.05$), rather than those with the Met/Met genotype ($X^2=0.008, p=.92$). No significant interaction of genotype by treatment condition was seen for percentage of cocaine-negative urine specimens collected, however

Regarding outcomes during follow-up, the mixed effect regression did not indicate a statistically significant genotype by treatment interaction during follow-up, rather, treatment groups maintained the gains they made during treatment rather than showing further change. For example, percentage of days of abstinence from cocaine during the follow-up show a similar pattern to the within-treatment data, with best outcomes overall among those with a Val allele who were assigned to CBT4CBT (CBT4CBT Met/Met=69%, CBT4CBT Val=84%; TAU Met/Met=80%, TAU Val=74%; treatment by genotype ($F(df=3,76)=1.74, p=.19$).

Modified Stroop task

Sixty-three individuals in the genetic sample completed the modified Stroop task prior to and after completing treatment. Results indicate a genotype by treatment interaction over time, at a trend level ($F(df\ 1,63)=3.3, p=.07$). This is illustrated in Figure 3; for clarity of presentation, the figure includes change in reaction time to cocaine-related words across time, as there was very little change over time for the neutral words by gene or treatment condition. As shown, the greatest reduction over time appears to occur among the individuals carrying a Val allele assigned to CBT4CBT compared with TAU, suggesting less attentional bias to cocaine related words following treatment with CBT4CBT.

Discussion

Our evaluation of relationship of the *COMT* genotype to response to CBT4CBT versus standard treatment alone in this sample of cocaine-dependent methadone maintained individuals suggests the following. First, there was an overall effect of genotype over time, with greater reductions over time for those carrying a Val allele compared to those with the Met/Met genotype by the end of the 6 month follow-up. Second, analyses of treatment

condition by genotype suggests this may have been accounted for by relatively good outcomes for those with a Val allele when assigned to CBT4CBT versus treatment as usual, who were more likely to attain three or more weeks of continuous abstinence and had a higher percentage of days of abstinence from cocaine within treatment. Third, evaluation of pre- to posttreatment changes in the modified Stroop indicated greater reductions in attentional bias to the cocaine words over time for those carrying a Val allele who were assigned to CBT4CBT.

These are the first data from a randomized controlled trial to point to significant *COMT* by treatment (CBT4CBT versus TAU) interactions on primary outcomes. While consistent with those of Lonsdorf (30) in pointing to better response to CBT4CBT for Val carriers among individuals with panic disorder, these findings extend them by indicating that improved outcome for those with the Val allele occurred for those assigned to CBT4CBT relative to standard treatment. In terms of clinical implications, given the strong empirical support for CBT across a range of populations (9, 10) our data may suggest that the large group of individuals carrying a Val allele appear to respond particularly well to CBT. Understanding why this might be the case is worthy of further investigation.

Those with the Met/Met genotype would generally be considered as having a cognitive 'edge' related to dopamine signaling. However, the influence of *COMT* activity on cognitive function may depend on the type of cognitive task: The Met allele is associated with increased tonic DA transmission and better performance on cognitive tasks that require stable performance. This effect is presumably mediated by greater tonic stimulation of D₁ DA receptors in the PFC. In contrast, the Val allele is associated with increased phasic DA transmission and better performance on tasks that require cognitive flexibility. This cognitive effect of Val allele is proposed to be due to greater activation of striatal D₂ type DA receptors. (28, 29)

It is possible that the greater cognitive flexibility associated with the Val allele may be associated with improved learning and retention of new behavioral and cognitive strategies and hence greater ability to avoid or resist cocaine use. This is partially supported by the data from the modified Stroop task, which, while preliminary and based on small sample size did suggest less distraction by the cocaine-related words over time for those with a Val allele assigned to CBT4CBT versus treatment as usual.

Strengths and limitations

This study had several strengths, including random assignment to treatment, utilization of a standardized, validated form of CBT4CBT, and availability of outcome data through the 6 month follow-up for 97% of the sample. Moreover, (1) these analyses were based on an *a priori* hypothesis and (2) only one polymorphism was evaluated here, reducing the likelihood that these results were due to chance alone. However, several limitations should be noted. First, not all participants agreed to provide DNA samples, and it is possible that selection bias may affect these findings. On the other hand, the Hardy-Weinberg equilibrium was satisfied for the genetics sample, indicating the subsample was representative of the relative rates of genotypes in the general population. Second, the sample size was small, limiting power as well as our ability to conduct additional analyses exploring gender and

race effects. The genotype by treatment interaction was not significant for the urine toxicology outcome, but did show a similar pattern as the self-reported percent days of abstinence as well as the 21 or more days of abstinence marker. Finally, the sample was composed of cocaine-dependent methadone maintained individuals many with long histories of severe substance use. Hence the generalizability of these findings is unclear; moreover, the possible role of *COMT* in risk for, or maintenance of, cocaine- and opioid dependence is largely unknown and it is possible that the Val158Met polymorphism acts differently in different psychiatric populations.

Conclusions

Taken together, however, the results suggest that in this sample, individuals carrying a Val allele had particularly good response to CBT4CBT compared with treatment as usual. These findings were seen for cocaine outcomes, as well as a measure of attentional bias. Within the Val group, those assigned to CBT4CBT appeared to exert more cognitive control across time in that they were less likely to be distracted by cocaine words on the modified Stroop task. While preliminary, if borne out in future studies, this possible biomarker of response to CBT is worthy of future research.

CBT is becoming established as an effective and durable treatment across multiple psychiatric disorders, and genetic polymorphisms that play a role in executive function, cognitive control, and plasticity are emerging in several populations as predictors of response to pharmacotherapies and behavioral treatments. As suggested by Kandel (8), these data suggest the potential promise of linking advances in neuroscience with genotypes involved in executive functioning with behavioral therapies that have been demonstrated to be effective across several psychiatric conditions. Understanding how the addicted mind benefits from treatment is likely to require integration of cognitive science, genetics, and other emerging fields. This trial suggests the potential of integrating treatments of known efficacy with neurocognitive data to better understand changes that may reflect the learning, acquisition or practice of skills and strategies taught in CBT.

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Figure 1.

Data availability by treatment condition (CONSORT for genetic sample)

Figure 2.
Rates of participants attaining three or more weeks of continuous abstinence during weeks 0-8 by treatment condition and genotype.

Figure 3.
Modified Stroop, reaction time to cocaine words by treatment condition and genotype.

Table 1

Baseline demographics and treatment assignment by genotype

	Met/Met n=17	Met/Val or Val/Val n=64	Total n=81	df	f	p
<i>Categorical variables</i>						
Assigned to CBT4CBT ^a , number (%)	8 (47.1)	30 (46.9)	38 (46.9)	1	0	0.99
Treatment as usual (TAU) ^b	9 (52.9)	34 (53.1)	43 (53.1)			
Number (%) female	11 (64.7)	41 (64.1)	52 (64.2)	1	0.00	0.96
Race						
Caucasian	13 (76.5)	37 (57.8)	50 (61.7)	1	3.06	0.38
African-American	4 (23.5)	19 (29.7)	23 (28.4)			
Hispanic	0 (0)	7 (10.9)	7 (8.6)			
Multiracial	0 (0)	1 (1.6)	1 (1.2)			
Completed high school	13 (76.5)	45 (70.3)	58 (71.6)	1	0.25	0.62
Unmarried or living alone	17 (100)	56 (87.5)	73 (90.1)	1	2.36	0.12
Unemployed	16 (94.1)	57 (89.1)	73 (90.1)	1	0.39	0.54
Referred by criminal justice system	1 (5.9)	12 (18.8)	13 (16)	1	1.65	0.20
On public assistance	15 (88.2)	50 (78.1)	65 (80.2)	1	0.87	0.35
Lifetime alcohol use disorder ²	12 (70.6)	47 (74.6)	59 (73.8)	1	0.11	0.74
Lifetime major depression	6 (35.3)	30 (31.3)	26 (32.1)	1	0.10	0.75
<i>Continuous variables (mean + standard deviation)</i>						
Methadone dose at baseline	92.9+28.2	81.4+26.1	83.9+26.8	1,78	2.51	0.12
Days paid for work in past 28	1.8+5.4	2.4+5.5	2.3+5.5	1,79	0.15	0.70
Age	43.7+9.2	42.1+9.6	42.4+9.5	1,79	0.39	0.54
Days of cocaine use, past 28	11.7+9.4	15.2+9.1	14.5+9.2	1,79	1.93	0.17
Days of heroin use, past 28	1.8+4.9	1.8+5.2	1.8+5.1	1,79	0.00	0.97
Days of marijuana use, past 28	3.5+7.5	2.8+6.9	3.0+7.0	1,79	0.15	0.70
Days of cigarette use, past 28	26.4+6.8	25.4+7.8	25.6+7.6	1,79	0.21	0.64
Days of alcohol use, past 28	.4+.5	.4+.5	.4+.5	1,79	0.39	0.54

	Met/Met n=17	Met/Val or Val/Val n=64	Total n=81	df	f	p
Age of first cocaine use	19.7+5.5	19.6+5.0	19.6+5.1	1,79	0.01	0.94
Years of regular cocaine use	12.4+6.0	12.0+9.4	12.1+8.8	1,79	0.02	0.90
ASI ^c Medical Composite	.53+.39	.37+.38	.40+.38	1,79	2.48	0.12
ASI Employment Composite	.74+.28	.79+.23	.78+.24	1,79	0.61	0.44
ASI Alcohol Composite	.04+.07	.05+.13	.05+.12	1,79	0.10	0.75
ASI Cocaine Composite	.67+.18	.64+.25	.65+.24	1,79	0.15	0.70
ASI Legal Composite	.06+.17	.08+.16	.07+.16	1,79	0.10	0.75
ASI Family Composite	.15+.19	.10+.12	.11+.14	1,79	2.27	0.14
ASI Psychological Composite	.17+.23	.15+.19	.15+.20	1,79	0.24	0.62
Shipley IQ	101.7+12.3	97.1+11.3	97.9+11.6	1,74	1.98	0.16

Note.

^aCBT4CBT¹ indicates computerized cognitive behavioral therapy plus standard treatment.

^bTAU indicates standard methadone maintenance treatment.

^cASI indicates Addiction Severity Index; composite scores range from 0 to 1, where higher scores indicate severity/higher level of problems.

Table 2
Process indicators and primary cocaine use outcomes by treatment condition and genotype (N=81)

	CBT4CBT ^a				TAU ^b				Genotype × Treatment			
	Met/Met n=8		Met/Val or Val/Val n=30		Met/Met n=9		Met/Val or Val/Val n=34		Genotype F p		F p	
												df
<i>Process indicators</i>												
Days in treatment, mean (SD) ^c	45.6 (16.6)		47.4 (17.7)		52.0 (8.5)		44.7 (20.3)		0.31	0.58	0.85	3,77
CBT4CBT modules completed ^d	4.1 (2.0)		5.1 (2.6)		n/a		n/a		0.95	0.34	n/a	1,36
Homework assignments completed ^e	2.4 (2.0)		3.1 (2.3)		n/a		n/a		0.70	0.41	n/a	1,36
<i>Primary continuous outcomes</i>												
Percent days abstinent from cocaine, self-report	54.5 (27.5)		69.8 (28.1)		73.4+28.4		49.4+32.2		0.29	0.59	5.80	3,76
Percent urine specimens testing negative for cocaine metabolites	16.6 (31.1)		36.2 (38.1)		24.1 (32.5)		18.5 (26.4)		0.59	0.44	1.90	3,72

Note.

^a CBT4CBT indicates computerized cognitive behavioral therapy plus standard treatment.

^b TAU indicates treatment as usual/standard treatment.

^c For days in treatment, maximum = 56.

^d Maximum possible number of CBT4CBT modules = 7

^e Maximum possible homework assignments completed = 6.