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Disruption of Reward Processing in Addiction
An Image-Based Meta-analysis of Functional Magnetic Resonance Imaging Studies

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IMPORTANCE Disrupted reward processing, mainly driven by striatal dysfunction, is a key characteristic of addictive behaviors. However, functional magnetic resonance imaging (fMRI) studies have reported conflicting results, with both hypoactivations and hyperactivations during anticipation and outcome notification of monetary rewards in addiction.

OBJECTIVE To determine the nature and direction of reward-processing disruptions during anticipation and outcome notification of monetary rewards in individuals with addiction using image-based meta-analyses of fMRI studies.

DATA SOURCES Relevant publications were identified searching PubMed (inclusion until March 2015) using the following terms: reward, fMRI, substance use, cocaine, cannabis, opiates, alcohol, nicotine, smokers, gambling, gamblers, gaming, and gamers. Authors of included articles were contacted to obtain statistical fMRI maps.

STUDY SELECTION Inclusion criteria: reward task involving monetary reward anticipation and/or outcome; participants showing addictive behaviors; and healthy control group. Exclusion criteria: participants aged younger than 18 years; recreational substance use or gambling; participants at risk for addictive behaviors; and studies using the same patient data as other included studies.

DATA EXTRACTION AND SYNTHESIS Study procedures were conducted in accordance with the Meta-analysis of Observational Studies in Epidemiology guidelines. Using Seed-based *d* Mapping software, meta-analyses were performed using random-effect nonparametric statistics with group whole brain *T*-maps from individual studies as input. Analyses were performed across all addictions and for substance and gambling addictions separately.

MAIN OUTCOMES AND MEASURES Group differences (individuals with addiction vs control individuals) in reward-related brain activation during reward anticipation and outcome using fMRI (planned before data collection).

RESULTS Twenty-five studies were included in the meta-analysis, representing 643 individuals with addictive behaviors and 609 healthy control individuals. During reward anticipation, individuals with substance and gambling addictions showed decreased striatal activation compared with healthy control individuals. During reward outcome, individuals with substance addiction showed increased activation in the ventral striatum, whereas individuals with gambling addiction showed decreased activation in the dorsal striatum compared with healthy control individuals.

CONCLUSIONS AND RELEVANCE Striatal hypoactivation in individuals with addiction during reward anticipation and in individuals with gambling addiction during reward outcome is in line with the reward-deficiency theory of addiction. However, the combination of hypoactivation during reward anticipation and hyperactivation during reward outcome in the striatum of individuals with substance addiction may be explained using learning-deficit theory.

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Supplemental content

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Addictive behaviors, including substance use disorders (SUD) and gambling disorder (GD), are among the most common and devastating psychopathologies.[1] Substance use disorders have a prevalence of about 4% to 5% in the general population[2] and account for about 20% of all disability-adjusted life years attributed to mental conditions worldwide.[1] Additionally, 21% of the world population uses tobacco products, which are associated with many serious health risks including dependence.[3] The prevalence of GD in developed countries ranges between 1% and 3% and has been rising in college students in the past decade.[4,5] Despite the growing number of evidence-based treatments for SUD, their efficacy remains moderate, with relapse rates for SUD of about 50% to 60% within 1 year.[6,7] For GD, only few evidence-based treatments are available, and their efficacy has been mostly disappointing.[8] Insight into the neural mechanisms of addictive behaviors is crucial to target the pathophysiology of addiction and develop more effective treatments.

One of the key findings on the pathophysiology of addictive behaviors is a dysfunction of so-called cortico-striatal reward pathways, including the ventral striatum (VS) and the medial prefrontal cortex (mPFC).[9-14] In the past decade, reward processing in individuals with addictive behaviors has been extensively studied by measuring brain reactivity to nondrug rewards (mostly monetary) using functional magnetic resonance imaging (fMRI). However, the nature and direction of reward-processing dysfunction remain unclear because some studies show hypoactivations and others hyperactivations (or nondeviant activations) in the VS of individuals with addictive behaviors compared with healthy control individuals (for reviews, see Balodis et al,[9] Hommer et al,[10] Diekhof et al,[12] and Leyton et al[14]).

These conflicting results have been interpreted in the context of 3 dominant but largely incompatible theories, known as the reward deficiency syndrome (RDS) theory, impulsivity theory, and incentive sensitization theory. The RDS theory[15,16] posits that individuals with addictive behaviors have a general deficit in recruiting brain reward pathways, resulting in chronic hypoactivation of these circuits and supposedly reduced pleasurable experience from rewards. Addictive behaviors, such as substance use or gambling, are consequently initiated to compensate for this reward deficiency and stimulate brain reward centers, including the VS. In contrast, the impulsivity theory[17-19] suggests that addictive behaviors are the result of a generally hyperactive brain reward system. Individuals with a hyperreactive brain reward system may show a strong response to cues predicting potential rewards, thereby explaining novelty seeking, impulsivity, and the continuous drive and motivation to obtain substances of abuse or other potentially rewarding stimuli. Finally, the incentive sensitization theory[13] proposes that individuals with addictive behaviors show a bias toward addiction-related cues owing to acquired incentive salience of these cues. As a result, addictive behaviors and associated cues hijack the brain-reward system, resulting in relatively increased VS responses to drug cues and relatively reduced VS responses to nondrug cues in SUD.[20] Note that in the case of GD, where money is the reward of interest, the incentive sensitization theory would predict an increased response to gambling/monetary cues in the brain reward pathways.

Key Points

Question What are the nature and direction of pathophysiologic reward-processing disruptions in the brain during anticipation and outcome notification of monetary rewards in individuals with addiction to substances and gambling?

Findings In this image-based meta-analysis of neuroimaging studies, striatal activation during reward anticipation was decreased among individuals with addiction compared with those in control groups. During reward outcome, substance-addicted individuals showed increased activation in the ventral striatum, whereas gambling-addicted individuals showed decreased activation in the dorsal striatum, compared with controls.

Meaning These findings provide evidence for both reward deficiency and learning-deficit theories in addiction.

Several issues may explain inconsistencies in fMRI findings on reward-processing deficits in addiction. First, different studies report activity during reward anticipation vs reward outcome phases, which reflect distinct processes with different relevance for addictive behaviors.[21] For example, reward anticipation often results from the perception of appetitive cues whose incentive value is innate or has been learned by association with positive outcomes, thus reflecting motivational processes.[22] In contrast, reward outcome is more relevant for learning processes and signaling the salience of new stimuli.[21,23] While reward anticipation and reward outcome processes can be separately investigated using fMRI, the dominant addiction theories remain relatively vague in specifying which of these processes are specifically affected in the course of addiction. A second reason for previously reported inconsistencies relates to the fact that reward-processing deficits in addicted individuals are likely phase dependent. For example, normalization of structural abnormalities within the reward neuro-circuitry has been described after prolonged abstinence.[24,25] Furthermore, often co-occurring psychiatric disorders, such as attention-deficit/hyperactivity disorder, also affect reward processing and have been associated with reward-anticipation deficits.[26,27]

To unravel contradictory findings on reward-processing dysfunction in addiction, we performed a quantitative image-based meta-analysis of the fMRI literature, using whole-brain group *T* maps from individual studies as input. This approach is more powerful than traditional coordinate-based meta-analyses in that it uses the full image information, including effect sizes and between-subject variance, in addition to activation localization.[28,29] Moreover, image-based meta-analyses partly address issues of limited sample sizes in individual studies and variability in data analysis. We performed separate analyses focusing on reward anticipation vs outcome processing in both individuals with SUD and individuals with GD. Substance use disorders and GD were both included to test the hypothesis of shared neurobiological

mechanisms underlying substance and behavioral addictions. Finally, we explored the influence of psychiatric comorbidities and different stages of the addiction cycle on reward processing.[9,10,30] We hypothesized that a blunted reward response (mainly in VS and mPFC) in both SUD and GD supports the RDS theory, while an increased reward response supports the impulsivity theory. In contrast, a blunted reward response in SUD individuals, together with an increased response in GD individuals, supports incentive sensitization theory, given the monetary nature of the task paradigms.

Methods

Inclusion of Studies

A literature search was performed using PubMed. Search terms "reward" and "fMRI" had to co-occur with 1 of the following keywords: substance use, cocaine, cannabis, opiates, alcohol, nicotine, smokers, gambling, gamblers, gaming, and gamers. Reference lists of included studies were screened to identify additional relevant articles. Inclusion criteria were inclusion in PubMed before March 1, 2015, participants showing addictive behavior, reward task involving monetary reward anticipation and/or outcome, and inclusion of a healthy control group. Exclusion criteria were inclusion of adolescents (aged younger than 18 years); target population with recreational substance use, gambling or gaming, or at-risk groups (eg, addicted family members); and studies using the same patient data as other included studies. Meta-analysis of Observational Studies in Epidemiology guidelines for meta-analyses of observational studies[31] were followed in this study. Next, corresponding authors were contacted via e-mail requesting to share their group-level fMRI data, ie, *T* maps representing monetary reward anticipation and/or outcome contrasts, both within groups (SUD, GD, and healthy control) and between-groups (SUD vs healthy control and GD vs healthy control).

Analyses

Seed-Based *d* Mapping

Our image-based meta-analyses were performed using the software Seed-Based *d* Mapping (SDM, version 4.31, http://www.sdmproject.com, formerly "Signed Differential Mapping"). Seed-Based *d* Mapping allows us to perform voxel-based meta-analyses using full statistical images as input[29,32] and has been extensively validated in previous meta-analyses.[33-36]

Seed-Based *d* Mapping recreates voxel-level maps of effect sizes (Hedge's *d*) and their variances based on input *T* maps, thereby substantially increasing the sensitivity of voxel-based meta-analyses compared with coordinate-based methods.[28,29] Additionally, SDM offers the possibility to have both positive and negative values in the same map; this provides richer information and allows the computation of standard meta-analytic measures such as between-study heterogeneity. To evaluate cross-study convergence, a random-effect model is applied in which each study is weighted by the inverse of the sum of its variance plus the between-study variance. Thus, studies with larger sample sizes or lower variability have a stronger contribution. Meta-analytic effect sizes are then divided by their standard errors across studies, eventually leading to SDM *Z* maps. Given that the distribution of these *Z* values typically deviates from normality, a null distribution is empirically estimated using permutation statistics (ie, randomizations of effect sizes across voxels). Previous simulations have shown that a number as low as 20 permutations already leads to highly stable estimates.[29] To be on the safe side, all the analyses reported were based on 50 permutations. Finally, statistical thresholding is based on a voxel-wise uncorrected *P* value less than .005. It has been shown that in the context of presently used permutation statistics, such a threshold is equivalent to a corrected *P* value of .05 and provides an optimal balance between sensitivity and specificity.[29] This threshold was complemented by a required minimum cluster size of 10 voxels (approximately 80 mm^3) and a peak-level threshold of *Z* greater than 1 to further reduce the possibility of false positives.

Whole-Brain Analyses

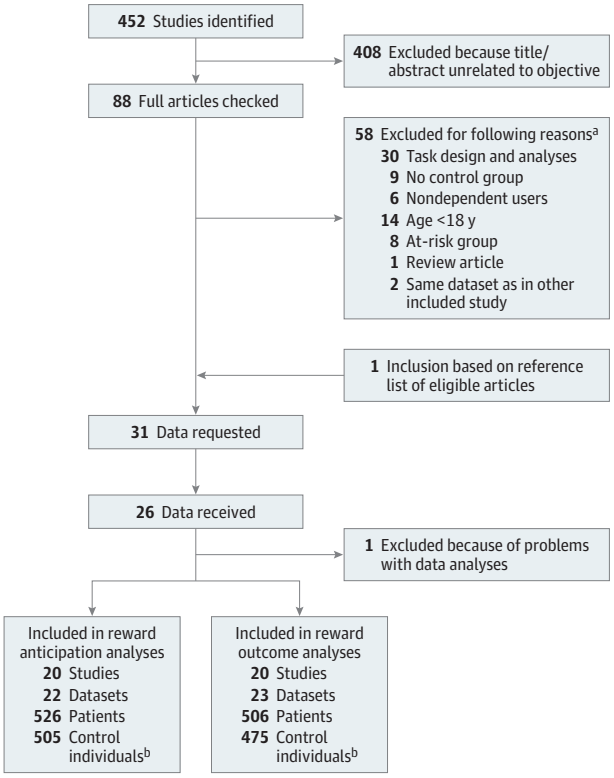
Primary analyses examined brain activity during reward anticipation and reward outcome in all individuals showing addictive behaviors vs healthy control individuals. For reward anticipation and reward outcome, included *T* maps were between-group comparisons of contrasts representing the anticipation/outcome of a monetary win vs the anticipation/outcome of a neutral, negative, or alternative event (see eTable 1 in the Supplement for specific contrasts included per study). To increase consistency across studies, some of the contrasts included in the analyses are not those reported in the original publication but additional contrasts obtained from the authors. Secondary analyses examined the same contrasts separately in individuals with SUD and individuals with GD (vs healthy control individuals). Statistical analyses were restricted to a custom gray-matter mask, following SDM recommendations. Although some of the collected *T* maps did not have full brain coverage (n = 5), all of them covered the key areas of interest including the striatum and mPFC.

The robustness of whole-brain results was examined using a jack-knife procedure, consisting of systematic repetitions of the meta-analyses described in previous paragraphs after excluding 1 study at a time. In the Results section, we report the number of overlapping jack-knife analyses as an index of replicability of the results.

Region of Interest Analyses

Region of interest analyses were performed to examine the contributions of individual studies and potential publication biases more closely. Regions of interest were defined functionally from whole brain maps and regional mean effect sizes, and variances for individual studies were extracted using the option integrated in SDM. These data were used to make forest plots and funnel plots illustrating striatal activation patterns during reward anticipation and outcome. In the forest plots, we categorized studies as a function of psychiatric comorbidities and phase of addiction to qualitatively assess whether the results might be potentially driven by some of these subgroups (see eMaterials in the Supplement for decision criteria regarding the categorization of studies).

Figure 1. Flowchart Outlining the Selection Procedure of Studies



[a] Studies could be excluded for multiple reasons.

[b] This number of control individuals reflects the number of unique control individuals. Some studies included 2 different addicted groups (eg, cannabis users and smokers) and 1 reference group of control individuals. Therefore, the number of datasets is higher than the number of studies.

Results

Included Studies and Sample Characteristics

The search resulted in 31 studies to be included in the meta-analyses (**Figure 1**). We received data from 26 studies (84%). One of these studies was excluded from the analyses because of technical problems. The remaining 25 studies[17,37-60] were included in the analyses; of these, 17 reported brain activation both during reward anticipation and outcome phases. Combined, these studies included 643 individuals with addictive behaviors (mean (SD) age, 33.5 (8) years; 527 men [82%]) and 609 unique healthy control individuals (mean (SD) age, 33.2 (8.5) years; 469 men [77%]). Across studies, individuals with addictive behaviors and healthy control individuals did not differ in terms of age and sex. Study-specific details including demographic information and type of addicted populations are shown in the **Table**.

In total, 20 studies were included in the analyses of brain activation during reward anticipation. Two of these studies included 2 addicted populations that were each compared with 1 healthy control group, leading to a final number of 22 data sets available for meta-analyses on reward anticipation. Twenty studies were included in the analyses of brain activation during reward outcome. Three of these studies included 2 addicted populations that were each compared with 1 healthy control group, leading to a final number of 23 data sets available for meta-analyses on reward outcome. See eTable 2 in the Supplement for the included studies and the number of participants per analysis specifically.

Meta-analytic Brain Imaging Results

Whole-brain maps of the main results are available online at http://neurovault.org/collections/1501.

Reward Anticipation Phase

We first examined group differences across all included studies, ie, across all addictions. The most striking group difference was observed in the bilateral striatum, in which individuals with addictive behaviors showed decreased responses during reward anticipation compared with healthy control individuals (**Figure 2**A). Further whole-brain analyses revealed that this pattern was present in individuals with SUD and in individuals with GD compared with their respective control groups when analyzed separately (Figure 2A). The extraction of effect sizes within significant striatal voxels revealed no gross abnormalities (**Figure 3**) except for 2 data sets presenting relatively large effect sizes (see the Sensitivity Analyses subsection). Other group differences were visible outside of the striatum including in the mPFC, anterior cingulate cortex, amygdala, orbitofrontal cortex, and dorsolateral prefrontal cortex (see eTables 3 and eTable 4 in the Supplement). *Z* maps showing brain activations separately for addicted and matched healthy control groups are reported in eFigure 1 in the Supplement.

Reward Outcome Phase

In contrast to the anticipation phase, individuals with addictive behaviors showed enhanced responses in the ventral striatum during reward outcome compared with healthy controls (Figure 2B). The extraction of effect sizes revealed no gross abnormalities (**Figure 4**). Importantly, further analyses showed that this pattern was mostly driven by individuals with SUD, who showed markedly enhanced activity in the ventral striatum (Figure 2B). In contrast, individuals with GD showed no significant differences in the ventral striatum compared with healthy control individuals, but decreased responses in the bilateral dorsal striatum (Figure 2B). Other whole-brain group differences, including findings in the orbitofrontal cortex, insula, and dorsolateral prefrontal cortex, are reported in eTable 5 and eTable 6 in the Supplement. *Z* maps showing brain activations separately for addicted and matched healthy control groups are reported in eFigure 2 in the Supplement.

Sensitivity Analyses

Using a jackknife procedure, we found that the striatal group differences observed during reward anticipation and outcome were replicated in virtually all jack-knife analyses, demonstrating the robustness of our results (eFigure 3 in the Supplement). We also reran our analyses after excluding the 2 data sets[57] with the largest striatal effect sizes (Figures 3 and 4), but the results remained qualitatively similar, suggesting that these data sets do not disproportionately influence our findings

Table. Participant Characteristics

Source	Type of Participants, No.	Age, Mean (SD)	Male Sex, No. (%)	Addiction Diagnosis and Severity	Active, Initial Abstinence, Prolonged Abstinence	Psychiatric Comorbidity[a]
Balodis et al,[37] 2012	GD (14); HC (14)	PG: 35.8 (11.7); HC: 37.1 (11.3)	PG: 10 (71); HC: 10 (71)	*DSM-IV* diagnosis GD	Active gambling	No current psychiatric comorbidity (self-report)
Beck et al,[38] 2009	ADI (19); HC (19)	ADI: 41.8 (6.8); HC: 41.7 (9.0)	ADI: 19 (100); HC: 19 (100)	*DSM-IV* and *ICD-10* diagnoses alcohol dependence	Initial abstinence alcohol	No current psychiatric comorbidity (SCID)
Bjork et al,[39] 2008	ADI (23); HC (23)	ADI: 33.8 (9.1); HC: 34.7 (9.7)	ADI: 12 (52) ; HC: 12 (52)	*DSM-IV* diagnosis alcohol dependence	Initial abstinence alcohol	Psychiatric comorbidity present (interview)
Bjork et al,[17] 2012	ADI (29); HC (23)	ADI: 30.9 (8.2); HC: 30.1 (5.9)	ADI: 15 (52); HC: 15 (52)	*DSM-IV* diagnosis alcohol dependence	Initial abstinence alcohol	Psychiatric comorbidity present (interview)
Bustamante et al,[40] 2014	CoDI (17); HC (18)	CoDI: 37.4 (8.2); HC: 37.5 (5.9)	CoDI: 17 (100); HC: 18 (100)	*DSM-IV* diagnosis cocaine dependence	Prolonged abstinence cocaine	No current psychiatric comorbidity (SCID)
Choi et al,[41] 2012	GD (15); HC (15)	GD: 27.9 (6.9); HC: 26.6 (4.3)	GD: 15 (100); HC: 15 (100)	*DSM-IV* diagnosis GD	Active gambling	No current psychiatric comorbidity (SCID)
Cousijn et al,[42] 2012	CaDI (32); HC (41)	CaDI: 21.4 (2.3); HC: 22.2 (2.4)	CaDI: 21 (66); HC: 26 (63)	Heavy cannabis use ≥10 d/mo for ≥2 y	Active cannabis	No current psychiatric comorbidity (MINI)
Fauth-Bühler et al,[43] 2014	GD (80); HC (89)	GD: 37.4 (9.1); HC: 36.2 (9.4)	GD: 80 (100); HC: 89 (100)	*DSM-IV* diagnosis GD	Mix gambling	Psychiatric comorbidity not excluded (SCID)
Filbey et al,[44] 2013	CaDI (59); HC (27)	CaDI: 23.5 (6.4); HC: 30.3 (10.1)	CaDI:46 (78); HC: 5 (18)	*DSM-IV* diagnosis cannabis dependence (58%); *DSM-IV* diagnosis cannabis abuse (10%); all: heavy cannabis use; ≥4 d/wk for ≥6 mo	Initial abstinence cannabis	Psychiatric comorbidity not excluded (SCID)
Goldstein et al,[45] 2007	CoDI (16); HC (13)	CoDI: 42.8 (4.6); HC: 37.6 (6.8)	CoDI: 12 (75); HC: 9 (69)	*DSM-IV* diagnosis cocaine dependence (56%); *DSM-IV* diagnosis cocaine abuse (38%); *DSM-IV* diagnosis past poly-substance abuse (6%)	Mix cocaine	Psychiatric comorbidity not excluded (interview)
Hägele et al,[46] 2014	ADI (26); HC (54)	ADI: 43.3 (7.0); HC: 37.7 (11.1)	ADI: 25 (96); HC: 41 (76)	*DSM-IV* and *ICD-10* diagnoses alcohol dependence	Mix alcohol	No current psychiatric comorbidity (SCID)
Jansma et al,[47] 2013	NDI (10); HC (11)	NDI: 21.2 (2.5); HC: 25.6 (7)	NDI: 10 (100); HC: 11 (100)	At least 10 cigarettes per d; FTND mean (SD): 4.3 (0.95)	Active nicotine, initial abstinence cannabis	No current psychiatric comorbidity (MINI)
Jia et al,[48] 2011	CoDI (20); HC (20)	CoDI: 38.6 (9.3); HC: 35.3 (10.2)	CoDI: 12 (60); HC: 12 (60)	*DSM-IV* diagnosis cocaine dependence	Mix cocaine	Psychiatric comorbidity present (SCID)
Martin et al,[49] 2014	NDI (16); HC (17)	NDI: 31.4 (9.8); HC: 33.7 (10.3)	NDI: 6 (38); HC: 8 (47)	At least 10 cigarettes per d; FTND mean (SD): 3.6 (1.9)	Active nicotine	No current psychiatric comorbidity (self-report)
Miedl et al,[50] 2010	GD (12); OG (12)	GD: 39.5 (9.3); OG: 33.4 (8.0)	GD: 12 (100); OG: 12 (100)	*DSM-IV* diagnosis problem gambling (42%); *DSM-IV* diagnosis GD (58%)	Active gambling	No current psychiatric comorbidity (assessment unknown)
Nestor et al,[51] 2010	CaDI (14); HC (14)	CaDI: 22.1 (4.5); HC: 23.1 (4.5)	CaDI: 12 (86); HC: 11 (79)	Heavy cannabis use 5-7 d/wk for ≥2 y	Mix cannabis	No current psychiatric comorbidity (assessment unknown)
Patel et al,[52] 2013	CoDI (42); HC (47)	CoDI: 38.5 (7.1); HC: 34.6 (9.0)	CoDI: 24 (58); HC: 26 (56)	*DSM-IV* diagnosis cocaine dependence	Active cocaine	No current psychiatric comorbidity (SCID)
Romanczuk-Seiferth et al,[53] 2015	GD (18); ADI (15); HC (17)	GD: 33.6 (9.5); ADI: 45.4 (10.2); HC: 37.4 (11.8)	GD: 18 (100); ADI: 15 (100); HC: 17 (100)	GD: *DSM-IV* and *ICD-10* diagnosis GD; ADI: *DSM-IV* and *ICD-10* diagnosis alcohol dependence	Active gambling, initial abstinence alcohol	No current psychiatric comorbidity (interview)
Rose et al,[54] 2014	NDI (28); HC (28)	NDI: 32.7 (10.0); HC: 30.1 (7.8)	NDI: 13 (46); HC: 16 (57)	18-40 cigarettes per d; FTND mean (range): 5.9 (3-9)	Active nicotine	No current psychiatric comorbidity (assessment unknown)
De Ruiter et al,[55] 2009	GD (19); NDI (19); HC (19)	GD: 34.3 (9.4); NDI: 34.8 (9.8); HC: 34.1 (9.3)	GD: 19 (100); NDI: 19 (100); HC: 19 (100)	GD: All in treatment for gambling problems; 79% lifetime *DSM-IV* diagnosis GD; NDI: at least 15 cigarettes per d; FTND mean (SD): 5.1 (1.5)	Initial abstinence gambling, initial abstinence nicotine	GD: Psychiatric comorbidity present NDI: No current psychiatric comorbidity (DIS)
Sescousse et al,[56] 2013	GD (18); HC (20)	GD: 34.1 (11.6); HC: 31.0 (7.3)	GD: 18 (100); HC: 20 (100)	*DSM-IV* diagnosis GD	Active gambling	No current psychiatric comorbidity (structured interview)
Van Hell et al,[57] 2010	CaDI (14); NDI (14); HC (13)	CaDI: 24 (4.4); NDI: 25 (4.5); HC: 24 (2.7)	CaDI: 13 (93); NDI: 11 (79); HC: 11 (85)	CaDI: Heavy cannabis use ≥150 joints last year and ≥1500 joints lifetime; NDI: ≥5 cigarettes per d (mean = 13)	Initial abstinence cannabis, active nicotine	No current psychiatric comorbidity (interview)

(continued)

Table. Participant Characteristics (continued)

Source	Type of Participants, No.	Age, Mean (SD)	Male Sex, No. (%)	Addiction Diagnosis and Severity	Active, Initial Abstinence, Prolonged Abstinence	Psychiatric Comorbidity[a]
Van Holst et al,[58] 2012	GD (15); HC (16)	GD: 38.0 (13.4); HC: 34.9 (12.0)	GD: 15 (100); HC: 16 (100)	*DSM-IV* diagnosis GD	Initial abstinence gambling	No current psychiatric comorbidity (CIDI)
Van Holst et al,[59] 2014	ADI (19); HC (19)	ADI: 42.5 (10.4); HC: 40.4 (10.7)	ADI: 19 (100); HC: 19 (100)	*DSM-IV* diagnosis alcohol dependence	Initial abstinence alcohol	No current psychiatric comorbidity (CIDI)
Yip et al,[60] 2014	CaDI (20); HC (20)	CaDI: 26.7 (9.8); HC: 29.2 (10.3)	CaDI: 20 (100); HC: 20 (100)	*DSM-IV* diagnosis cannabis dependence	Mix cannabis	Psychiatric comorbidity present (SCID)

Abbreviations: ADI, alcohol dependent individuals; CaDI, cannabis dependent individuals; CIDI, World Mental Health Composite International Diagnostic Interview; CoDI, cocaine dependent individuals; DIS, diagnostic interview schedule; *DSM-IV*, *Diagnostic and Statistical Manual of Mental Disorders (Fourth Edition)*; FTND, Fagerström Test for Nicotine Dependence; GD, gambling disorder; HC, healthy control individuals; *ICD-10*, *International Statistical Classification of Diseases and Related Health Problems, Tenth Revision*; MINI, Mini International Neuropsychiatric Interview; NDI, nicotine dependent individuals; SCID, Structured Clinical Interview for *DSM* Disorders; SOGS, South Oaks Gambling Screen; SUD, substance use disorder.

[a] Nicotine as comorbidity allowed in all studies.

(eFigure 4 in the Supplement; but see also eFigure 5 in the Supplement for additional results that appear in the ventral striatum during reward anticipation when excluding these data sets). Similarly, excluding the 5 studies[17,38,46,57,59] with partial brain coverage did not qualitatively affect our main results (eFigure 6 in the Supplement). Finally, funnel plots in the striatum showed no evidence of publication bias for reward anticipation and weak indication of publication bias for reward outcome (eFigure 7 in the Supplement). For both anticipation and outcome, the results observed in the striatum remained significant after Duval and Tweedie's trim and fill analyses.

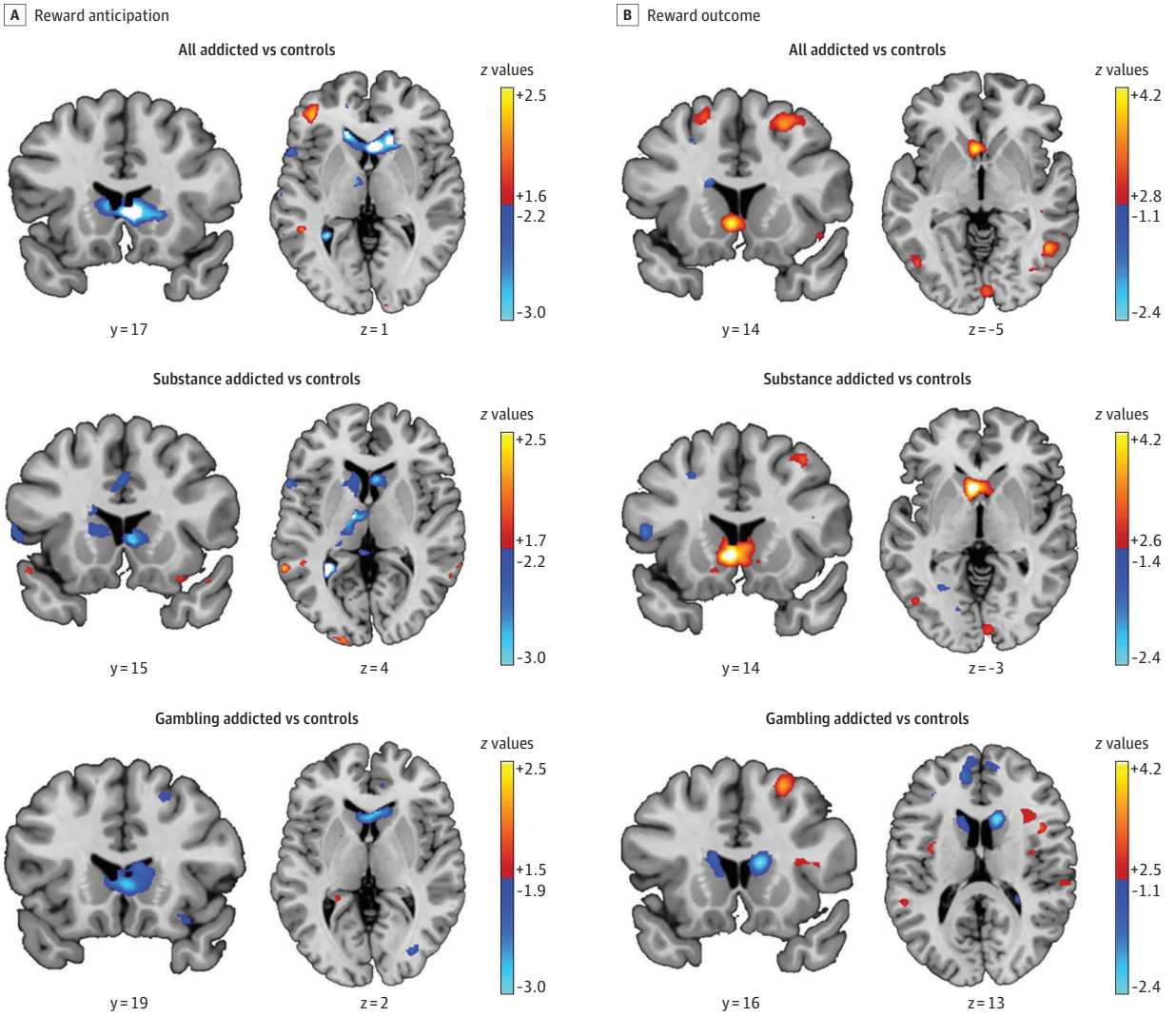
Discussion

Using image-based meta-analyses of fMRI studies, we observed decreased striatal activation during reward anticipation across individuals with SUD and individuals with GD in comparison with healthy controls. During reward outcome, individuals with SUD showed increased activation in the VS, whereas individuals with GD showed decreased activation in the dorsal striatum. Within the SUD group, similar striatal activation patterns were observed across substances (Figures 3 and 4). In this section, we examine how these results align with the main reward theories of addiction (ie, RDS, impulsivity, and incentive sensitization theories) that are most often invoked to interpret findings in the included studies. We also discuss whether addiction phase and comorbidity influence these findings.

Reduced striatal activation during reward anticipation in both individuals with SUD and individuals with GD has been previously suggested in narrative reviews.[9,15] Reduced striatal activation during reward anticipation is in line with the RDS theory[15] (suggesting reduced striatal responses to non-addiction-related rewards) and is also in line with the incentive sensitization theory in individuals with SUD (suggesting reduced striatal responses to non-drug-related cues but increased responses to drug-related cues).[13] However, reduced anticipatory striatal activity in individuals with GD is inconsistent with incentive sensitization theory, which would have predicted increased striatal responses to monetary cues, which can be considered to be gambling related. However, some authors have argued that the cues used in tasks such as the monetary incentive delay task are abstract and unfamiliar to individuals with GD and thus unlikely to elicit enhanced striatal activations.[14] According to this view, exhaustive testing of the incentive sensitization theory in GD would thus require the use of more gambling-specific cues, such as chips or gambling scenes, that have been shown to increase striatal responding in GD.[61] During reward outcome, the increased VS activation observed in individuals with SUD is difficult to reconcile with the RDS theory but is in line with the impulsivity theory.[17,18] However, the observed hypoactivation in the striatum during reward anticipation is inconsistent with the impulsivity theory.

In sum, none of the 3 currently dominant reward theories on addiction can fully account for the observed striatal activation patterns in SUD during reward anticipation and outcome. However, our findings may be interpreted in the context of temporal difference reinforcement learning theories.[23,62] According to temporal difference reinforcement learning theories, increased activation in striatal regions is observed in response to unexpected rewards, reflecting so-called reward prediction errors. During the process of learning, these striatal responses gradually shift to cues predicting upcoming rewards. Reduced anticipatory striatal activation in SUD may thus reflect a learning deficit, ie, failure to predict monetary rewards. As a result, reward prediction errors would remain abnormally large, reflected by enhanced VS activity during reward outcome in individuals with SUD. Our findings in individuals with SUD may therefore reflect impaired reinforcement learning processes in this population. Interestingly, previous studies in patients with alcohol dependence have reported a link between altered learning mechanisms and impairments in the functioning of the striatum and its functional coupling with the dorsolateral prefrontal cortex .[63,64] One may speculate that reward-learning deficits in individuals with addiction contribute to impaired decision making, eventually resulting in the tendency to select addiction-related behaviors at the expense of non-addiction-related activities, possibly owing to sensitization processes.[20] However, most of the experimental paradigms used in the included studies did not require explicit cue-outcome learning. Future studies should investigate whether the observed findings in this meta-analyses generalize to explicit learning situations.

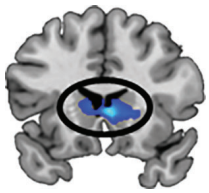
Figure 2. Whole Brain Meta-analytic Results

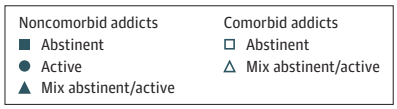


Brain regions showing significant differences between individuals with addiction and healthy control individuals during monetary reward anticipation (A) and monetary reward outcome (B). Enhanced activity in individuals with addiction is shown in red/yellow, while decreased activity is shown in blue/turquoise. Group differences are shown for all individuals with addiction versus healthy control individuals (top), individuals with substance addiction versus healthy control individuals (middle) and individuals with gambling addiction versus healthy controls (bottom). Functional *Z* maps are overlaid on the Colin 27 anatomical template and thresholded at $P < .005$ and $k \geq 10$ (equivalent to a corrected *P* value of .05).

During reward outcome, individuals with SUD and GD did not show the same pattern of brain activation. While individuals with SUD showed increased VS responses, individuals with GD showed decreased activation in the dorsal striatum. The decreased striatal activation observed in individuals with GD during both monetary reward anticipation and outcome could be interpreted as support for the RDS theory[15] in GD. However, positron emission tomography studies have argued against a generally reduced functioning of the reward system in GD and have shown instead enhanced dopamine release during gambling or in response to an amphetamine challenge.[65,66] Therefore, we consider the differences in reward outcome processing between individuals with SUD and individuals with GD more likely to be owing to the monetary nature of the rewards used in the included studies. Monetary rewards are the core drivers of the addictive behavior in individuals with GD.[67] Importantly, the location of the decreased reward outcome response in GD in the dorsal rather than the ventral striatum might suggest that the monetary rewards were not necessarily appealing to individuals with GD. It has previously been suggested that activation of the dorsal striatum is more strongly related to arousal rather than reward.[21] Given that the rewards delivered in a typical fMRI experiment are usually less arousing than the highly salient monetary wins received during real-life gambling, individuals with GD may have been less aroused than healthy control individuals by these monetary rewards. Also, it has to be acknowledged that most GD studies did not control for comorbid SUD and vice versa. There-

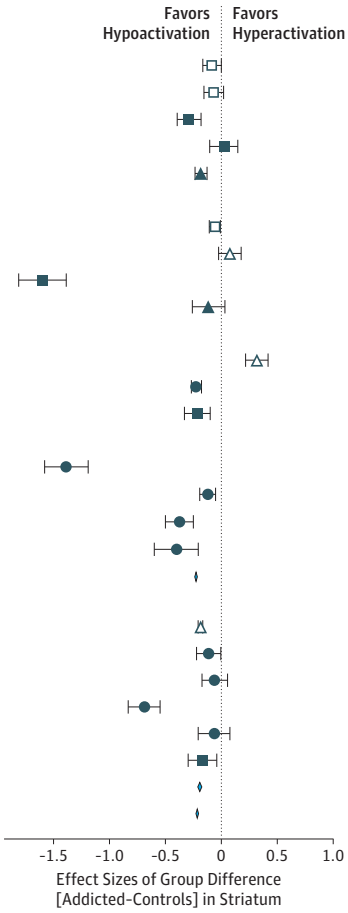
Figure 3. Forest Plot Illustrating Reward Anticipation Meta-analytic Results in the Striatum





Reward Anticipation

Substance Addiction	Mean Effect Size (Variance of Effect Size)
Alcohol	
Bjork et al,[17] 2012	-0.08 (±0.08)
Bjork et al,[39] 2008	-0.07 (±0.09)
Van Holst et al,[59] 2014	-0.29 (±0.11)
Romanczuk et al,[53] 2014	0.02 (±0.13)
Hagele et al,[16] 2014	-0.18 (±0.06)
Cannabis	
Filbey et al,[44] 2013	-0.06 (±0.05)
Yip et al,[60] 2014	0.08 (±0.10)
Van Hell et al,[57] 2010	-1.6 (±0.21)
Nestor et al,[51] 2010	-0.11 (±0.14)
Cocaine	
Jia et al,[48] 2011	0.32 (±0.10)
Patel et al,[52] 2013	-0.22 (±0.05)
Bustamante et al,[40] 2013	-0.22 (±0.12)
Nicotine	
Van Hell et al,[60] 2010	-1.39 (±0.20)
Rose et al,[54] 2013	-0.12 (±0.07)
Martin et al,[49] 2014	-0.37 (±0.12)
Jansma et al,[47] 2013	-0.40 (±0.20)
Average substance	-0.23 (±0.01)
Gambling addiction	
Fauth-Buhler et al,[43] 2014	-0.19 (±0.02)
Sescousse et al,[56] 2013	-0.11 (±0.11)
Romanczuk et al,[53] 2014	-0.06 (±0.11)
Choi et al,[41] 2012	-0.69 (±0.14)
Balodis et al,[37] 2012	-0.06 (±0.14)
Van Holst et al,[58] 2012	-0.17 (±0.13)
Average gambling	-0.19 (±0.01)
Average all studies	-0.21 (±0.006)

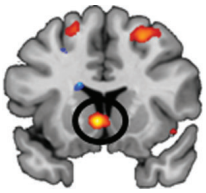


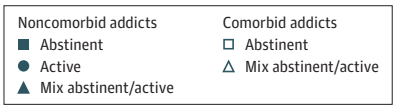
This forest plot shows the mean ±variance of effect sizes for group differences in the striatum estimated from individual studies during monetary reward anticipation. Note that this forest plot is shown for illustrative purposes because it reports effect size estimates in the striatal voxels that were found to be significant at the whole-brain level (these voxels are reproduced from Figure 2 and circled for convenience). The mean ±variance estimates across all studies, substance use disorder studies, and gambling disorder studies are shown with turquoise diamonds.

fore, the differences between individuals with SUD and individuals with GD as observed here might have even been blunted owing to this frequent comorbidity. These findings emphasize the need to go beyond the use of monetary rewards in fMRI studies, eg, using positive scenes, food, juice, or erotic stimuli.[56] This will help better understand differences and similarities in reward-processing disruptions among individuals with SUD and GD because money may be indirectly related to the availability of substances of abuse for individuals with SUD. Notably, only 1 study in GD controlled for the socio-economic status of participants.[56] It is unclear to what extent socio-economic status might affect the observed striatal responses to monetary rewards in individuals with GD in particular. This is a question that should be addressed in future studies. Finally, the subjective experience associated with the anticipation and consumption of various rewards should be evaluated because it may differ between healthy and addicted individuals.

While striatal regions largely dominate current reward theories in addiction, they obviously do not operate in isolation. Our image-based meta-analysis approach allowed us to investigate reward-processing activation throughout the brain. Both during reward anticipation and outcome, we observed differences between individuals with addiction and control individuals in other reward-related regions, such as the mPFC, anterior cingulate cortex, amygdala, orbitofrontal cortex, and insula, as well as in cognitive control regions such as the dorsolateral prefrontal cortex (see eTable 3 and eTable 6 in the Supplement for a complete overview). Similar to what we found in the striatum, activation in the mPFC was reduced in individuals with addiction during reward anticipation, which is in line with previous accounts suggesting that the striatum and

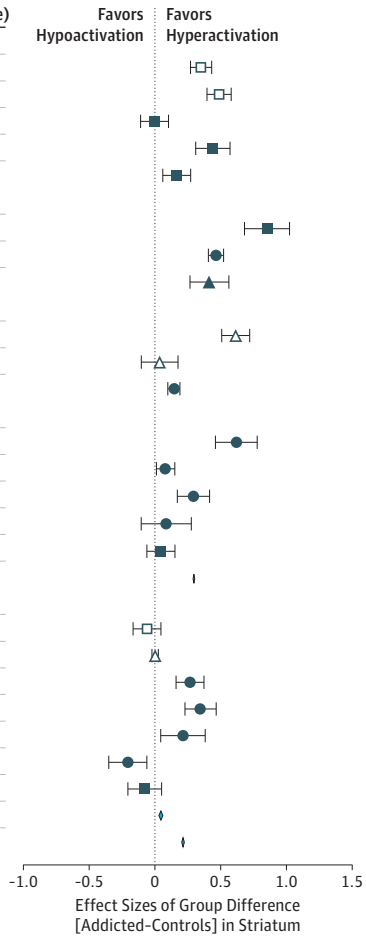
Figure 4. Forest Plot Illustrating Reward Outcome Meta-analytic Results in the Striatum





Reward Outcome

Substance Addiction	Mean Effect Size (Variance of Effect Size)
Alcohol	
Bjork et al,[17] 2012	0.35 (±0.08)
Bjork et al,[39] 2008	0.49 (±0.09)
Van Holst et al,[59] 2014	-0.001 (±0.11)
Romanczuk et al,[53] 2014	0.44 (±0.13)
Beck et al,[38] 2009	0.16 (±0.11)
Cannabis	
Van Hell et al,[57] 2010	0.86 (±0.17)
Cousijn et al,[42] 2013	0.47 (±0.06)
Nestor et al,[51] 2010	0.42 (±0.15)
Cocaine	
Jia et al,[48] 2011	0.62 (±0.11)
Goldstein et al,[45] 2007	0.04 (±0.14)
Patel et al,[52] 2013	0.15 (±0.05)
Nicotine	
Van Hell et al,[57] 2010	0.62 (±0.16)
Rose et al,[54] 2013	0.08 (±0.07)
Martin et al,[49] 2014	0.30 (±0.12)
Jansma et al,[47] 2013	0.09 (±0.19)
de Ruiter et al,[55] 2009	0.05 (±0.11)
Average substance	0.30 (±0.007)
Gambling addiction	
de Ruiter et al,[55] 2009	-0.06 (±0.11)
Fauth-Buhler et al,[43] 2014	0.005 (±0.02)
Sescousse et al,[56] 2013	0.27 (±0.11)
Romanczuk et al,[53] 2014	0.35 (±0.12)
Miedl et al,[50] 2010	0.22 (±0.17)
Balodis et al,[37] 2012	-0.20 (±0.14)
Van Holst et al,[58] 2012	-0.08 (±0.13)
Average gambling	0.05 (±0.01)
Average all studies	0.22 (±0.005)



This forest plot shows the mean ±variance of effect sizes for group differences in the striatum estimated from individual studies during monetary reward anticipation. Note that this forest plot is shown for illustrative purposes because it reports effect size estimates in the striatal voxels that were found to be significant at the whole-brain level (these voxels are reproduced from Figure 2 and circled for convenience). The mean ±variance estimates across all studies, substance use disorder studies, and gambling disorder studies are shown with turquoise diamonds.

mPFC operate together to monitor reward predictability, expectation, and salience.[12,68] Interestingly, activation in the amygdala was increased rather than decreased in individuals with addiction during reward anticipation. Given that the amygdala also plays a role in reward prediction and has a reciprocal influence on striatal activity,[69,70] future studies should focus on the functional coupling between these regions in the context of reward processing in addiction.[71]

Inconsistent findings in reward processing in addiction have often been attributed to the phase of the addiction cycle and/or presence of psychiatric comorbidities.[9] Distinguishing studies with individuals with active addiction from those with abstinent individuals does not seem to substantially influence our results (Figures 3 and 4), highlighting the stability of our findings regardless of the addiction phase. It has to be acknowledged that several studies do not clearly describe current substance use patterns or gambling activity and often include mixed samples of using and recently abstinent participants. Therefore, an effect of the addiction phase on reward processing cannot be entirely ruled out. Regarding psychiatric comorbidities, studies excluding comorbid participants seemed to show more consistent striatal hypoactivations during reward anticipation compared with studies that did not (Figure 3). Decreased striatal activity during reward anticipation in addiction is therefore not a mere consequence of comorbidity. Yet, it is clear that some of the most prevalent co-occurring conditions, such as attention-deficit/hyperactivity disorder, depression, and schizophrenia, are associated with alterations in striatal activity during reward anticipation in different directions.[26,72-74] Moreover, pharmacological treat-

ment of psychiatric conditions, eg, with bupropion, might also affect striatal reward processing.[75] Most studies included in the meta-analyses did not control for potential confounding effects of psychiatric comorbidities or pharmacological treatments. Of special interest here is comorbid nicotine dependence because most individuals with SUD and GD also use nicotine, which can affect reward-related brain activity. While most studies tried to reduce the potential confounding effects of acute nicotine use (by ensuring that participants did not smoke right before scanning), they did not address the potential confounding effects of nicotine withdrawal during scanning. Given the potentially confounding effects and high prevalence of psychiatric comorbidities, future studies on reward processing in addiction should pay particular attention to these issues and use (semi-)structured clinical interviews to assess psychiatric comorbidities.

A further limitation of this meta-analysis is the cross-sectional nature of the included studies, which hampers drawing conclusions about whether reward-processing deficits are a cause or a consequence of addictive behaviors. Some initial longitudinal studies have started investigating this issue,[76-78] but more longitudinal research is needed to formulate final conclusions.

Conclusions

To our knowledge, this study is the first to use an fMRI image-based meta-analysis approach to study addiction. The results show consistent hypoactivation during reward anticipation in the striatum across individuals with GD and SUD. During reward outcome, individuals with SUD showed increased VS activation, while individuals with GD showed decreased dorsal striatum activation. The observed activation patterns in individuals with addiction may fit best with theories on reinforcement learning. Future studies should further address issues related to the phase of addiction and psychiatric comorbidity in relation to reward-processing deficits in addiction.

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Concept and design: Luijten, Schellekens, Kühn, Sescousse.
Acquisition, analysis, or interpretation of data: All authors.
Drafting of the manuscript: Luijten, Schellekens, Sescousse.
Critical revision of the manuscript for important intellectual content: All authors.
Statistical analysis: Schellekens, Kühn, Sescousse.
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Study supervision: Luijten, Schellekens, Sescousse.

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