Remember the Future II: Meta-analyses and Functional Overlap of Working Memory and Delay Discounting

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Previously we showed that working memory training decreased the discounting of future rewards in stimulant addicts without affecting a go/no-go task. While a relationship between delay discounting and working memory is consistent with other studies, the unique brain regions of plausible causality between these two abilities have yet to be determined. Activation likelihood estimation meta-analyses were performed on foci from studies of delay discounting (DD = 449), working memory (WM = 452), finger tapping (finger tapping = 450), and response inhibition (RI = 450). Activity maps from relatively less (finger tapping) and more (RI) demanding executive tasks were contrasted with maps of DD and WM. Overlap analysis identified unique functional coincidence between DD and WM. The anterior cingulate cortex was engaged by all tasks. Finger tapping largely engaged motor-related brain areas. In addition to motor-related areas, RI engaged frontal brain regions. The right lateral prefrontal cortex was engaged by RI, DD, and WM and was contrasted out of overlap maps. A functional cluster in the posterior portion of the left lateral prefrontal cortex emerged as the largest location of unique overlap between DD and WM. A portion of the left lateral prefrontal cortex is a unique location where delay discounting and working memory processes overlap in the brain. This area, therefore, represents a therapeutic target for improving behaviors that rely on the integration of the recent past with the foreseeable future.

Key Words: Activation likelihood estimation (ALE), delay discounting, dorsal lateral prefrontal cortex (DLPFC), fMRI, temporal discounting, working memory

Excessive discounting of delayed reinforcers is a neurobehavioral process evident in a variety of disorders and suboptimal behaviors (1). Delay discounting, also referred to as temporal discounting or intertemporal choice, describes the decreasing value of a reinforcer as a function of the time or delay until its receipt (2). Excessive discounting of delayed reinforcers is evident in almost every form of drug dependence, problem gambling, obesity, attention-deficit/hyperactivity disorder, and schizophrenia and is correlated with a wide variety of important health behaviors. Furthermore, discounting rates are predictive of outcomes in clinical trials of behavior change (3), consistent with excessive discounting functioning as a trans-disease process (4).

Previous research has alluded to a functional relationship between delay discounting and working memory, identifying that the abilities to retain and manipulate transitory information are correlated (5,6). In addition, working memory training has been shown to improve clinical outcomes among individuals with attention-deficit/hyperactivity disorder (7,8), problem drinking (9), and schizophrenia (10). Moreover, in a recent manuscript entitled, "Remember the Future: Working Memory Training Decreases Delay Discounting Among Stimulant Addicts," we directly examined the effects of working memory training on the performance of various executive functioning tasks in stimulant-dependent individuals (11). In that study, participants performed delay discounting tasks of real and hypothetical rewards in addition to a go/no-go task examining response inhibition. Following working memory training, the discounting of real and hypothetical rewards was significantly reduced while response inhibition remained unaltered. These findings suggest a common functional relationship between delay discounting and working memory in the brain that is independent of processes engaged by response inhibition. The identification of brain areas that underscore this relationship will provide therapeutic targets for treating a variety of disease states where the processing of temporally relevant information is compromised.

While independent studies have identified brain areas engaged by delay discounting and working memory tasks, to date there has not been a controlled systematic analysis of the functional overlap between these tasks, adjusted for activity during other executive tasks. Independent studies suggest, however, that potential targets include the striatum (12) and frontal cortex (13) from studies of delay discounting tasks and portions of the bilateral frontal cortex (14,15) from studies of working memory. The goal of the present study is to use activation likelihood estimation (ALE), a well-validated and widely used quantitative meta-analysis technique (16,17), to provide the first comprehensive and controlled analysis of the unique functional relationship between delay discounting and working memory in the brain. First, we generated ALE functional brain maps from studies of 1) delay discounting, 2) working memory, 3) finger tapping, and 4) response inhibition. Next, a series of contrast and overlap analyses were performed to isolate unique brain areas involved in delay discounting and working memory.

Methods and Materials

Analytical Plan

A stepwise series of analyses were performed (graphical design in supporting information; Figure S1 in Supplement 1) using data from published neuroimaging data sets of delay discounting (18–35), working memory (36–62), finger tapping (63–97), and response inhibition (98–125) shown in Table 1. First,

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Table 1. fMRI Studies Included in Individual Meta-Analyses

Reference	*n*	Mean Age (Years)	Age Range (Years)	Contrasts of Interest (Experiments)	# Foci
Delay Discounting					
Christakou *et al.*, 2011 (20)	40	20	12–32	Delay > Immediate	11
				vmPFC Connectivity: Delayed Choice	15
Onoda *et al.*, 2011 (27)	30	22		Reward Prediction V(t) Related to Discounting Factor γ	12
Sripada *et al.*, 2011 (31)	20	29		Choose Later > Choose Earlier	15
Peters and Büchel, 2010 (29)	30	25		Episodic > Control	13
				Subjective Value Correlation: Episodic > Control	56
Bickel *et al.*, 2009 (18)	30	47	20–67	Discounting > Control: RMG	21
				Discounting > Control: HMG	20
				Discounting > Control: HML	23
Ersner-Hershfield *et al.*, 2009 (21)	22	26		Person x Time	02
				Time x Valence	01
				Person x Time x Valence	06
Peters and Büchel, 2009 (28)	22	26		Subjective Value Correlation of Delay Discounting: 1° GLM	25
				Subjective Value Correlation of Delay Discounting: Orthogonalized with Inverse Delay and Reward Magnitude: 2° GLM	19
				Reward Magnitude Correlation (Delay Discounting): 2° GLM	15
Pine *et al.*, 2009 (30)	24	23	19–28	Correlation with Discounting Factor (D)	22
				Correlation of Discounting Utility (V)	07
				Correlation of Choice Difficulty with Discounting Utility (ΔV)	07
				Correlation of Choice Difficulty with Discounting Utility (ΔV) Covary RT	02
				Correlation of Choice Difficulty with Discounting Factor (ΔD)	10
Xu *et al.*, 2009 (35)	20	25	22–29	Discounting Gains > Fixation	19
				Discounting Losses > Fixation	18
Hoffman *et al.*, 2008 (22)	42	36		Delay > Control (Magnitude Estimation)	11
Luhmann *et al.*, 2008 (24)	20	23	19–30	Delay > Immediate	05
Weber and Huettel, 2008 (33)	23	23	19–36	Delay > Control	05
Boettinger *et al.*, 2007 (19)	19	28		Subjective Choice Negatively Correlated with Impulsive Choice Ratio	01
Kable and Glimcher, 2007 (23)	10	21		Delayed Reward and Subjective Value: FIR-Type model	08
				Delayed Reward and Subjective Value: HRF-Type Model	14
Monterosso *et al.*, 2007 (26)	29	32		Discounting > No Choice: Hard Decision	06
				Discounting > No Choice: Easy Decision	03
Wittman *et al.*, 2007 (34)	13	26	18–39	Delay > Immediate	07
				(Delay > 1 year) > (Delay < 1 Year)	01
McClure *et al.*, 2004 (25)	14	21		Delay > Immediate: Beta Analysis	05
				Delay > Immediate: Delta Analysis	08
Tanaka *et al.*, 2004 (32)	20		22–34	Short Delay > No Delay	07
				Long Delay > No Delay	14
				Long Delay > Short Delay	15
Total Foci:					449
Working Memory					
Schmidt *et al.*, 2009 (60)	25	34		(1-, 2-, and 3-back) > 0-back: Males	08
	21	33		(1-, 2-, and 3-back) > 0-back: Females	06
Smits *et al.*, 2009 (62)	11	28		2-back > 0-back: Healthy Control Subjects	08
Drapier *et al.*, 2008 (40)	20	43	27–62	1-back > 0-back: Healthy Control Subjects	04
				2-back > 0-back: Healthy Control Subjects	06

Table 1. (continued)

Reference	*n*	Mean Age (Years)	Age Range (Years)	Contrasts of Interest (Experiments)	# Foci
				3-back > 0-back: Healthy Control Subjects	07
				1-back > 0-back: Healthy Relatives	02
				2-back > 0-back: Healthy Relatives	07
				3-back > 0-back: Healthy Relatives	05
Deckersbach *et al.*, 2008 (38)	17	26		2-back > Fixation	12
Dohnel *et al.*, 2008 (39)	16	61		2-back > Fixation	02
Frangou *et al.*, 2008 (42)	7	39		1-, 2-, and 3-back	11
Koppelstaetter *et al.*, 2008 (46)	15		25–47	2-back > 0-back	16
Sanchez-Carrion *et al.*, 2008 (59)	14	24		2-back > 0-back	16
				3-back > 0-back	18
Shamosh *et al.*, 2008 (61)	103	23	18–40	3-back > Fixation	01
Forn *et al.*, 2007 (41)	10			2-back > 0-back	10
Matsuo *et al.*, 2007 (49)	15	38		1-back > 0-back	04
				2-back > 0-back	02
Allen *et al.*, 2006 (36)	10		23–35	2-back > 0-back	06
Kumari *et al.*, 2006 (47)	13	33	18–55	1-back > 0-back	22
				2-back > 0-back	18
Meisenzahl *et al.*, 2006 (51)	12	34	28–38	2-back > Fixation	20
Ricciardi *et al.*, 2006 (58)	6	28		1-back > Rest	44
Malisza *et al.*, 2005 (48)	9			1-back > 0-back	13
Mendrek *et al.*, 2005 (52)	12	28		2-back > 0-back	12
Mendrek *et al.*, 2004 (53)	8			2-back > 0-back	08
Monks *et al.*, 2004 (54)	12	46		2-back > Baseline	17
Kim *et al.*, 2003 (45)	12	26	19–35	2-back > Control	08
Ragland *et al.*, 2002 (57)	11	32	21–53	1-back > 0-back	06
				2-back > 0-back	07
Haberecht *et al.*, 2001 (43)	14	15	7–20	1-back > 0-back	03
				2-back > 0-back	02
Pfefferbaum *et al.*, 2001 (56)	10	60	47–73	2-back > Rest	14
McAllister *et al.*, 1999 (50)	11	31		1-back > 0-back	05
Carlson *et al.*, 1998 (37)	7	21	17–23	1-back > 0-back	17
				2-back > 0-back	26
Owen *et al.*, 1998 (55)	6			1-back > 0-back	10
Jonides *et al.*, 1997 (44)	19			1-back > Control Button Press	03
				2-back > Control Button Press	22
				3-back > Control Button Press	24
Total Foci:					452
Finger Tapping					
Mostofsky *et al.*, 2009 (85)	13	11	8–12	Right Hand > Rest	09
				Left Hand > Rest	08
Hanakawa *et al.*, 2008 (73)	13	30	21–48	Tapping > Rest	13
Thaut *et al.*, 2008 (96)	12	26	20–36	3 Hz > 2 Hz	04
Gavazzi *et al.*, 2007 (70)	9	47		Flexion-Extension > Rest	03
Lissek *et al.*, 2007 (82)	33	25		Simple + Complex 1 + Complex 2 > Rest	48
Marchand *et al.*, 2007 (83)	14	48	21–65	Right Hand > Rest	03
				Left Hand > Rest	09

Table 1. (continued)

Reference	*n*	Mean Age (Years)	Age Range (Years)	Contrasts of Interest (Experiments)	# Foci
Cerasa *et al.*, 2006 (65)	11	63		Tapping > Fixation	02
Dimitrova *et al.*, 2006 (67)	12	29		Index Finger	11
Lehericy *et al.*, 2006 (80)	12	23	18–33	Simple > Rest	08
				Complex > Rest	27
Mostofsky *et al.*, 2006 (86)	11	10		Right Hand > Rest	03
				Left Hand > Rest	05
Riecker *et al.*, 2006 (89)	10	23	18–26	Index Finger	06
Aoki *et al.*, 2005 (63)	10	22	20–30	Index Finger > Rest	01
				Ring Finger > Rest	07
				Double Finger > Rest	12
De Luca *et al.*, 2005 (66)	7	37		Finger Tapping	04
Lacourse *et al.*, 2005 (78)	54	25		Novel > Rest	18
				Complex > Rest	17
Rounis *et al.*, 2005 (92)	8	37	20–68	Main Effects of Movement	17
Fox *et al.*, 2004 (69)	12	35	22–43	Finger Tapping > Rest	01
Lerner *et al.*, 2004 (81)	10		31–58	Finger Tapping > Rest	09
Wilson *et al.*, 2004 (97)	10	27		Finger Tapping > Rest	02
Elsinger *et al.*, 2003 (68)	13	63		Index Finger > Rest	05
Kuhtz-Buschbeck *et al.*, 2003 (77)	12	24	21–27	Simple, Right Hand > Baseline	04
				Complex, Right Hand > Baseline	08
				Simple, Left Hand > Baseline	09
				Complex, Left Hand > Baseline	12
Riecker *et al.*, 2003 (90)	8	24	19–32	Main Effect All Frequencies	08
Taniwaki *et al.*, 2003 (95)	10		24–29	Self-Initiated Movement > Rest	05
				Externally Triggered Movement > Rest	05
Langheim *et al.*, 2002 (79)	6	27	22–33	Bilateral Finger Tapping > Rest	05
Muller *et al.*, 2002 (87)	10	33		Finger Tapping > Rest	04
Rotte *et al.*, 2002 (91)	9	24		Fingers	16
Gosain *et al.*, 2001 (72)	5			Finger Tapping > Rest	02
Gerardin *et al.*, 2000 (71)	8	27	21–35	Motor Execution > Rest	24
Kawashima *et al.*, 2000 (76)	8		19–27	Cued Tapping > Rest	14
Sabatini *et al.*, 2000 (93)	6	59		Finger Tapping > Rest	10
Catalan *et al.*, 1999 (64)	13	52	41–52	Sequence 16 > Rest	12
Jancke *et al.*, 1999 (74)	6		22–37	Right Hand: 1 Hz > Rest	02
				Left Hand: 1 Hz > Rest	02
Joliot *et al.*, 1998 (75)	5	23		Finger Tapping > Rest	13
Mattay *et al.*, 1998 (84)	8	30		Dominant Hand Simple	12
Rao *et al.*, 1997 (88)	13	23	18–31	Synchronization-300 > Rest	03
				Continuation-300 > Rest	07
Samuel *et al.*, 1997 (94)	6	64	50–64	Unimanual Sequence > Rest	09
				Bimanual Sequence > Rest	12
Total Foci:					450
Response Inhibition					
Baglio *et al.*, 2011 (100)	11	67		Go > Fixation	22
				No-Go > Fixation	05
Mazzola-Pomietto *et al.*, 2009 (116)	16	35		Go > No-Go	07

Table 1. (continued)

Reference	*n*	Mean Age (Years)	Age Range (Years)	Contrasts of Interest (Experiments)	# Foci
Welander-Vatn *et al.*, 2009 (125)	28	38	18–38	Go/No-Go > Fixation	12
McNab *et al.*, 2008 (117)	11	24	22–34	No-Go > Go	06
Suskauer *et al.*, 2008 (123)	25	11	8–13	No-Go > Fixation	07
Langenecker *et al.*, 2007 (112)	17	34		Go	10
				No-Go	08
Simmonds *et al.*, 2007 (122)	30	11	8–12	Go	05
				No-Go	10
Aron and Poldrack, 2006 (99)	5	29		Go > Null Event	21
Brown *et al.*, 2006 (102)	10	26	22–26	No-Go Response > Fixation	19
Bohland and Guenther, 2006 (101)	13	29	22–50	Go > No-Go	40
Durston *et al.*, 2006 (104)	11	15	13–19	Go > No-Go: Healthy Control Subjects	02
				No-Go > Go: Healthy Control Subjects	09
	11	14	11–20	Go > No-Go: Unaffected Siblings	03
				No-Go > Go: Unaffected Siblings	05
Pessiglione *et al.*, 2006 (120)	39		19–37	Go/No-Go	07
Rubia *et al.*, 2006 (121)	23	28	20–43	Go/No-Go: Adults	11
	29	15	10–17	Go/No-Go: Adolescents	04
Altshuler *et al.*, 2005 (98)	13	31		No-Go > Go	04
Maltby *et al.*, 2005 (115)	14	37		No-Go	05
Durston *et al.*, 2003 (103)	7	9	6–9	Go > No-Go	08
Mostofsky *et al.*, 2003 (119)	48	27		Primary Go Effects	04
				Primary No-Go Effects	03
Garavan *et al.*, 2003 (106)	16	31	18–46	Task-Related Performance	12
				No-Go	07
Maguire *et al.*, 2003 (114)	06		22–30	Go/No-Go > Fixation	06
Durston *et al.*, 2002 (105)	10	28		Go > No-Go	10
Garavan *et al.*, 2002 (107)	14	30	19–45	No-Go	16
Watanabe *et al.*, 2002 (124)	11	25	19–40	Go	05
				No-Go	05
Liddle *et al.*, 2001 (113)	16	30		Go > Baseline	32
				No-Go > Baseline	19
Menon *et al.*, 2001 (118)	14	24	17–41	Go > Rest	07
Kiehl *et al.*, 2000 (109)	14	28		Errors of Commission	04
				No-Go	08
				Errors of Commission vs. Correct Rejects	02
				Go	12
Konishi *et al.*, 1999 (110)	6		21–31	No-Go	01
Konishi *et al.*, 1998 (111)	5		20–31	Go	09
				No-Go	19
Kawashima *et al.*, 1996 (108)	9		19–21	Go/No-Go > Control	39
Total Foci:					450

FIR, finite-impulse response; fMRI, functional magnetic resonance imaging; GLM, general linear model; HMG, hypothetical money gain; HML, hypothetical money loss; HRF, hemodynamic response function; RMG, real money gain; RT, reaction time; vmPFC, ventromedial prefrontal cortex.

four independent activation likelihood estimation meta-analyses were conducted on studies of 1) delay discounting, 2) working memory, 3) finger tapping, and 4) response inhibition. Second, a series of contrast analyses were performed to adjust ALE brain maps of delay discounting and working memory for activity during tasks of finger tapping and response inhibition. This contrast step was crucial for isolating a more specific relationship between delay discounting and working memory. Finger tapping was envisioned as a task engaging minimal executive processes but sharing features with many other tasks (e.g., attention, visual processing, motor responses). Response inhibition was envisioned as a task requiring more executive processes and was limited to studies utilizing the go/no-go task. The decision to only include go/no-go studies was motivated by our previous observation that working memory training altered discounting rates but not response inhibition as measured by the go/no-go task. So, the current design was optimized for 1) identifying a behaviorally relevant functional relationship between delay discounting and working memory, and 2) eliminating the possibility of observing effects due to differences between go/no-go and other response inhibition tasks. Lastly, a series of overlap analyses were performed to reveal unique and overlapping brain areas involved in delay discounting and working memory.

Inclusion Criteria and Identification of Publications

All studies used in the meta-analyses were subject to identical inclusion criteria: experiments or contrasts must 1) result from an analysis including healthy control participants; 2) use functional magnetic resonance imaging (fMRI) or positron emission tomography imaging techniques to probe brain activity; 3) use the entire brain as a search volume; and 4) report imaging results in standardized Montreal Neurologic Institute or Talairach three-dimensional coordinate-based space.

Publications were identified using the pre-existing ALE BrainMap database (www.brainmap.org/pubs), as well as a series of MEDLINE (U.S. National Library of Medicine, Bethesda, Maryland) searches with keywords relevant to each study type (e.g., delay discounting fMRI and working memory fMRI) and synonyms, acronyms, and combinations of search terms (e.g., intertemporal choice and functional magnetic resonance imaging). As relevant publications were identified, their reference sections were analyzed for additional publications to be included.

Due to relatively fewer imaging publications for studies of delay discounting, initial efforts focused on identifying delay discounting studies that met inclusion criteria. Of these studies, contrasts or parametric analyses were selected that specifically sought to isolate brain responses for processing information about the future (e.g., later choices > now choices and correlations with discounting factors). In an effort to maximize power and the number of studies included, distinctions were not made between various types of discounting (e.g., discounting of gains versus losses). While this and other distinctions are relevant, in this initial report, we chose to focus on more general brain activity related to future considerations. Of note, one delay discounting study (Table 1, number 6) correlated discounting measures calculated outside of an fMRI scanner with brain activity from an fMRI task examining the evaluation of an individual's current versus future self. This contrast was included because it used time-relevant information strongly correlated with discounting rates to isolate brain activity. As an additional control step, meta-analyses were matched on the number of three-dimensional locations (i.e., foci) contributing to each analysis. For delay discounting, a total 37 contrasts reporting 449 foci were included. Working memory included 41 contrasts

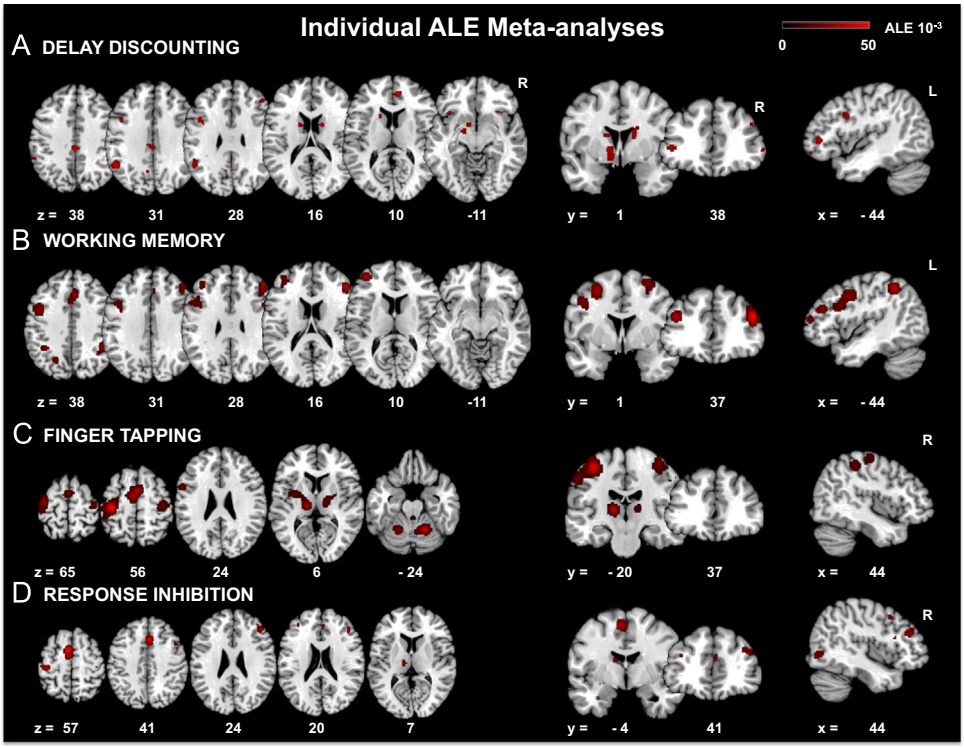

Figure 1. Significant false discovery rate corrected ($p < .05$) activation likelihood estimation (ALE) values for tasks of (**A**) delay discounting, (**B**) working memory, (**C**) finger tapping, and (**D**) response inhibition. Activation likelihood estimation values for left (L) and right (R) hemispheres are presented on the Montreal Neurologic Institute standard space template.

reporting 452 significant foci. Studies of finger tapping resulted in 49 contrasts and 450 foci, and response inhibition included 43 contrasts reporting 450 foci.

Activation Likelihood Estimation

Each of the four ALE meta-analyses used the Turkeltaub *et al.* (126) corrected ALE algorithm for minimizing within-experiment and within-group effects (see Supplement 1 for more detail). For each analysis, ALE values were computed for all focal locations from contributing contrasts. A null distribution ALE statistic was calculated with full-width half at maximum values empirically determined by the sample size of each contributing study. Values were then subjected to a false discovery rate (FDR) algorithm. Individual meta-analyses were performed with the FDR Pn adjustment at a $p < .01$ and a minimum extent threshold cluster threshold of 100 mm^3.

ALE Contrasts

To examine the degree of convergence, a series of contrast analyses were performed. Due to difficulty in interpreting the subtraction of ALE maps (e.g., subtractions resulting in values of zero), *Z* score maps were generated for each contrast of interest in a two-step process. First, two single and one pooled ALE analysis was performed (similar to the individual ALE analyses described above). The three resultant activity maps corresponded to two individual sets (e.g., 1 = delay discounting and 2 = finger tapping) and one pooled set (e.g., 3 = delay discounting + finger tapping) of foci for each contrast of interest. These three maps were then combined and analyzed to generate *Z* score maps. Next, *Z* score maps of finger tapping and response inhibition were contrasted with maps of delay discounting and working memory: 1) DD > FT; 2) WM > FT; 3) DD > RI; and 4) WM > RI. Individual and pooled ALEs were generated with FDR Pn adjustment at $p < .05$ with a minimum extent threshold of 100 mm^3. For *Z* score contrasts, 10,000 *p* value permutations were used with FDR Pn adjustment at $p < .05$ and a minimum extent threshold of 100 mm^3.

Spatial Overlap

Lastly, a series of overlap analyses were performed using the maps obtained from the contrast analyses. Contrasted maps of delay discounting and working memory were overlaid to reveal activity in unique and coincident brain areas. Overlap maps were then examined individually and combined in an omnibus analysis. The centroid locations for overlapping clusters were identified and *Z* scores were examined.

For visualizations, the structural Montreal Neurologic Institute template provided by BrainMap was used (Colin27_T1_seg_MNI.nii, www.brainmap.org/ale). Functional ALE and *Z* score results were overlaid using MRIcron (version 12/2009; www.mccauslandcenter.sc.edu/mricro/mricron/install.html). Centroid visualization and isolation was performed with Mango software (version 2.5, http://ric.uthscsa.edu/mango/).

Results

Individual Activation Likelihood Estimation Meta-Analyses

All individual ALE results are presented in Figure 1 and Table S1 in Supplement 1. During delay discounting, activity was observed in several limbic structures (Figure 1A), including the left medial globus pallidus and bilateral caudate, as well as the right putamen and left thalamus. Clusters were also observed in the bilateral temporal lobe. Posterior brain activations were observed

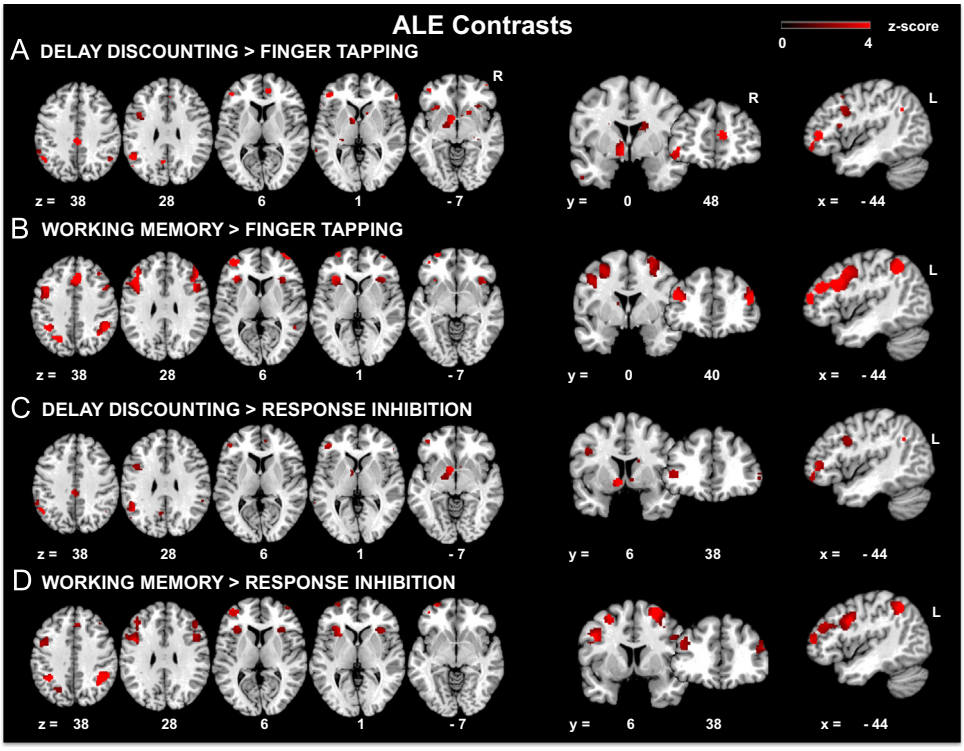

Figure 2. Significant false discovery rate corrected ($p < .05$) results showing activity for delay discounting and working memory contrasted with that of finger tapping (**A**, **B**) and response inhibition (**C**, **D**). *Z* score values for left (L) and right (R) hemispheres are presented on the Montreal Neurologic Institute standard space template. ALE, activation likelihood estimation.

Table 2. Overlapping ALE Clusters of Delay Discounting and Working Memory Contrasted with Finger Tapping and Response Inhibition

Delay Discounting and Working Memory > Finger Tapping and Response Inhibition								
#	Volume (mm^3)	x	MNI y	z	Overlap Centroid *Z* Score	Side	Brain Area	BA
1	979	−43	10	29	3.58	L	IFG/Lateral Prefrontal Cortex	9
3	16	−43	44	5	1.14	L	IFG/Lateral Prefrontal Cortex	10
4	42	−29	22	−5	1.91	L	Anterior Insula	
5	91	−41	48	−9	3.07	L	IFG/Lateral Prefrontal Cortex	47

ALE, activation likelihood estimation; BA, Brodmann area; IFG, inferior frontal gyrus; L, left; MFG, middle frontal gyrus; MNI, Montreal Neurologic Institute.

in bilateral superior parietal cortex, as well as posterior cingulate cortex. Additionally, several clusters were observed throughout the frontal lobe. Activity was observed in bilateral anterior insula, the anterior cingulate cortex (ACC), and throughout the inferior and middle frontal cortex, with the largest frontal activity clusters observed in the left frontal cortex.

Activity during working memory was also observed in several neocortical structures (Figure 1B). Activations were present in bilateral inferior and superior parietal cortices, with relatively larger spatial extents observed in working memory than delay discounting (WM: left = 7648 mm^3 and right = 5216 mm^3 vs. DD: left = 144 mm^3 and right = 184 mm^3). Several frontal lobe structures were also recruited during working memory. These included the ACC, as well as bilateral inferior, middle, and superior cortices. Unlike delay discounting, during working memory, clusters were not observed in more limbic brain structures.

Activation likelihood estimation results for finger tapping are presented in Figure 1C. With the exception of the ACC, there was a lack of activity in the prefrontal cortex during finger tapping. Activity was observed, however, in several movement-related brain areas. These areas included bilateral precentral and post-central gyri, as well as portions of the thalamus, putamen, and cerebellum.

Activity during response inhibition is presented in Figure 1D. During response inhibition, clusters were observed throughout the prefrontal cortex. Similar to the other tasks examined, activity was present in the ACC. Activity was also observed in bilateral middle and superior frontal cortices, with the largest extent of activity observed in the right lateral prefrontal cortex. Clusters were also present in the striatal caudate, the superior parietal cortex, and portions of the cerebellar cortex and occipital lobe.

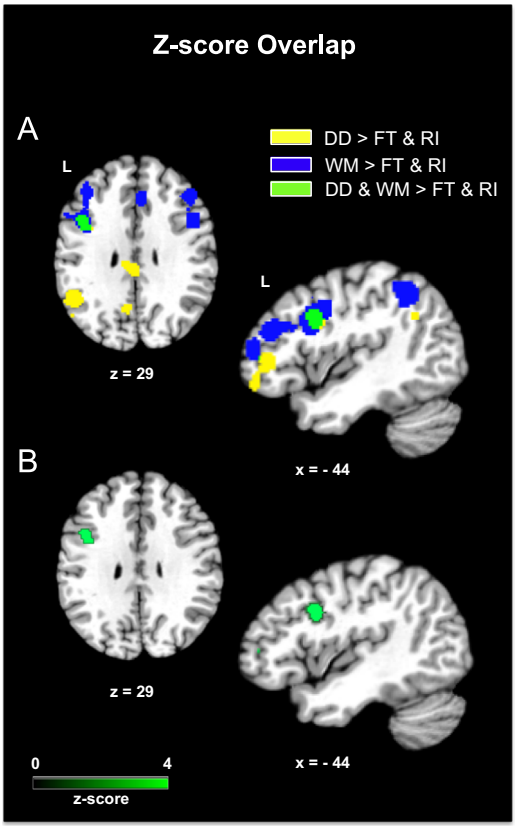

Figure 3. Combined and individual overlaps in activity maps of delay discounting (DD) and working memory (WM), contrasted with finger tapping (FT) and response inhibition (RI). Maps show activity in the left (L) and right hemispheres for (**A**) delay discounting (yellow) and working memory (blue), as well as functional overlap between the two tasks (green). (**B**) Exclusive functional overlaps of DD and WM.

ALE Contrasts

Results from ALE contrast analyses are presented in Figure 2 and Table S2 in Supplement 1. Following the contrasts of delay discounting with finger tapping (Figure 2A) and response inhibition (Figure 2C), activity was observed in both the ventral and dorsal striatum. Activity was also observed in bilateral dorsal parietal cortex and the medial prefrontal cortex. The largest clusters were present in the left lateral prefrontal cortex. The contrasts of working memory with finger tapping (Figure 2B) and response inhibition (Figure 2D) also resulted in several activity clusters throughout the brain. These clusters were in bilateral anterior insula and bilateral superior parietal cortex, and several clusters were observed in bilateral middle and superior frontal cortices. Similar to delay discounting, the largest activity clusters were present in the left hemisphere (Figure 2; x = −44). Of note, contrasting delay discounting and working memory with response inhibition resulted in the removal of activity clusters in the right lateral prefrontal cortex.

ALE Overlap

Overlaid *Z* score maps from ALE contrasts are shown in Figure 3 and Table 2 (with additional results in Figure S2 and Table S3 in Supplement 1). Overlays show contrasted activity specific to delay discounting (yellow) and working memory (blue), as well as contrasted activity shared by both tasks (green). Frontal lobe activity for delay discounting was more ventral to that observed for working memory (Figure 3A). Activity specific to delay discounting was observed in the posterior cingulate, while activity for working memory was observed in medial prefrontal cortex, coincident with the ACC. Relatively small clusters shared between delay discounting and working memory (< 100 mm^3) were observed in the left middle frontal cortex, anterior insula, and inferior frontal gurus. A larger overlapping cluster (979 mm^3)

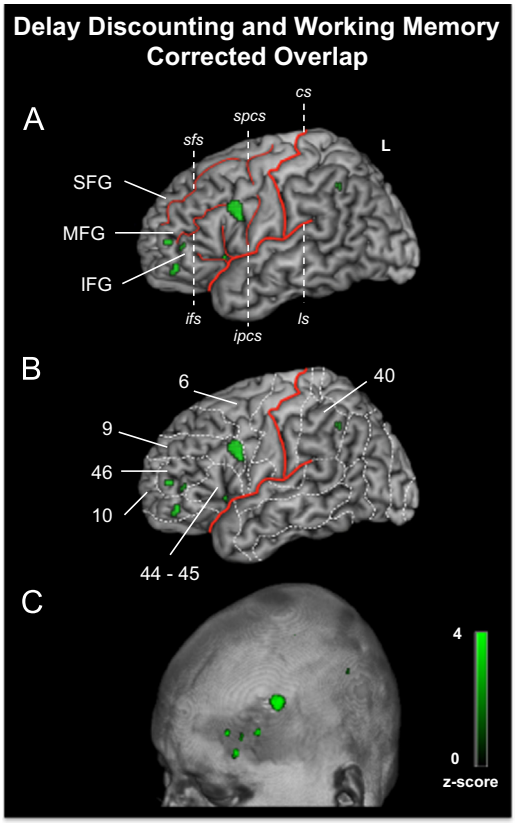

Figure 4. Location of exclusive functional overlaps. Figure shows overlaps of delay discounting and working memory activity from Figure 3B projected on three-dimensional infinite-depth Montreal Neurologic Institute anatomical templates (i.e., glass brains). (**A**) Functional overlaps on brain marking the left (L) hemisphere locations of the superior frontal gyrus (SFG), middle frontal gyrus (MFG), and inferior frontal gyrus (IFG). Sulci are the superior frontal sulcus (sfs), superior precentral sulcus (spcs), central sulcus (cs), inferior frontal sulcus (ifs), inferior precentral sulcus (ipcs), and lateral sulcus (ls). (**B**) Functional overlaps on brain showing relevant Brodmann area locations. (**C**) Functional overlaps projected on Montreal Neurologic Institute whole-head template.

was revealed in the left lateral prefrontal cortex (Figure 3B). This activity cluster was identified as a portion of the inferior frontal gyrus located in the posterior extent of Brodmann area 9 (Figure 4). For reference, Figure 4 displays contrast overlaps between delay discounting and working memory imposed on full-depth allowed, brain extracted and full head structural volumes.

Discussion

While a behavioral relationship between the discounting of delayed reinforcers and working memory has been observed previously, the potential brain regions of plausible causality that overlap both conditions have yet to be determined. The present analysis identified brain areas of functional overlap during tasks of delay discounting and working memory, corrected for activity in other tasks. First, matched activation likelihood estimation meta-analyses confirmed previous reports that delay discounting (12) and working memory (13) engage limbic and neocortical structures, including the striatum, insula, cingulate, and portions of the frontal lobe. Next, ALE activity maps from studies of finger tapping and response inhibition were used to further isolate activity during tasks of delay discounting and working memory. Lastly, overlap analyses revealed that delay discounting and working memory share a large cluster of activity lateralized in the left prefrontal cortex. Based upon these results, we posit that this portion of the left prefrontal cortex is distinctively qualified, through its executive functioning effort, to provide functions common to delay discounting and working memory that may account for a behavioral relationship.

Activation likelihood estimation activity maps of finger tapping and response inhibition were contrasted with maps of delay discounting and working memory to yield more specific results, as opposed to simply overlaying ALE results. This step was important, given our previous observation that working memory training did not change performance on a go/no-go task (11). As expected, finger tapping resulted in robust activations in several movement-related brain areas including precentral and postcentral gyri, thalamus, and cerebellum. Largely, finger tapping did not result in activity in more executive-related brain areas. This was with the exception of the anterior cingulate cortex, which consistent with its role in attention and performance monitoring (127–132), was engaged by all tasks. Correspondingly, in contrasting activity between tasks, ACC activity was largely removed from maps, with the exception of maps of working memory, which retained a unique cluster in the medial prefrontal cortex. Unlike finger tapping, response inhibition produced activity in bilateral middle prefrontal cortex and dorsal lateral prefrontal cortex (DLPFC). This is consistent with the relatively larger executive demands of the go/no-go task (107,133,134), as well as other conflict-monitoring tasks (135–137).

Interestingly, following contrasts of response inhibition with delay discounting and working memory, previously observed clusters in the right DLPFC for all tasks were removed. This result suggests that there are processes unique to response inhibition, delay discounting, and working memory that rely on functions within the right DLPFC. This activity plausibly reflects a more general executive demand shared by these three tasks. For example, greater activity in the right DLPFC is associated both with increasing task speed and cognitive load in tasks of executive functioning (138). Together, results from the contrast analyses highlight two main points: 1) with the exception of activity in the ACC, activities during delay discounting and working memory are largely independent from that of finger tapping; and 2) response inhibition, delay discounting, and working memory all engage portions of the right DLPFC, with more robust activity observed for working memory.

Overlap analyses revealed that delay discounting and working memory independently engaged superior and lateral portions of the parietal and frontal cortices. This parietal-frontal network has been demonstrated as essential for bottom-up and top-down integration of various memory components, including mnemonic processing (139); the storage, retrieval, and manipulation of long-term memories (140); and interactions between attention and working memory (141–143). This is consistent with our observation that working memory tasks resulted in more robust function in these areas compared with delay discounting. Interestingly, a recent electroencephalography study revealed that activity in posterior portions of this network is associated with the prospective memory that guides attention according to previously formed intentions (144).

The omnibus overlap analysis revealed that the largest area shared between delay discounting and working memory was in the left lateral prefrontal cortex. This activity cluster was located more posterior than the F3 and AF3 regions cited as the DLPFC in

electroencephalography studies (145). However, it is consistent with the posterior extent of Brodmann area 9 (146), which represents the most posterior extent of the DLPFC. This cluster is directly adjacent to the inferior frontal junction, which has also been highlighted for its role in top-down executive processes and cognitive control (147–149). Topographically, the observed location is potentially in two distinct cortical circuits, the dorsal cortical and the ventral cortical. The dorsal cortical circuit is linked to the dorsal anterior cingulate, the dorsomedial prefrontal cortex, and the dorsal anterolateral prefrontal cortex. This circuit supports the intentional regulation executive functions, such as attention and planning (150). In contrast, the ventral cortical circuit supports more the affective modulation of attentional performance (151). This cortical circuit includes the orbitofrontal cortex, amygdala, anterior insula, ventral striatum, medial thalamus, and paralimbic regions of the hippocampus. Based on previous descriptions and the cognitive nature of the tasks examined, it is likely that delay discounting and working memory largely work together through the former circuit to assist ongoing executive functions.

Lateral PFC and Executive Function

The lateral PFC is active during decision making and is particularly active when considering the rational costs and benefits of alternatives (150). It has been consistently identified as activated in studies of working memory and hypothesized to provide specialization through the active monitoring and manipulation of task-relevant information (14). It has also been shown to be active during delay discounting tasks but not modulated by parameters such as length of delay, choice preference, individual discounting rate, or reward magnitude (25,152,153). A recent transcranial magnetic stimulation (TMS) study, however, demonstrated that right DLPFC function modulates impulsivity levels and reward value calculations at different time scales (154). Of particular relevance to the current study, another TMS study found that disrupting the left, but not the right, DLPFC increased choices of immediate rewards over larger delayed rewards, providing causal evidence for a neural lateral-prefrontal cortex-based self-control mechanism in delay discounting (155). These converging lines of evidence, together with the current results, suggest a neural intersection for working memory constraints and abnormally high discounting rates. Furthermore, they posit that the left lateralized PFC is uniquely qualified to underlie executive processes shared between delay discounting and working memory. A potential mechanism for this relationship warrants further investigation, however, as the previously observed relationship between dopamine D1 binding potentials and working memory improvement found in other brain areas has not been observed in this region (156).

In terms of the competing neurobehavioral decision systems hypothesis, the impulsive system (comprised of evolutionarily older limbic structures) and the executive system (consisting of the evolutionarily young PFC) work in concert for optimal decision making (157,158). When either or both of these systems are functioning suboptimal (i.e., hypoactive or hyperactive), decision making becomes impaired. Imaging studies of both delay discounting and working memory have observed behavioral impairments associated with greater hypoactivity in the prefrontal cortex. Hypofrontal activity is also associated with compromised executive abilities in various disease states, including schizophrenia (159) and major depression (160). In a recent study, prefrontal hypoactivity during delay discounting was observed in methamphetamine-abusing populations, compared with control subjects (161). This is consistent with rodent studies showing that repeated self-administration of cocaine decreases basal levels of PFC activity (162). In the case of delay discounting and working memory, hypoactivity in the left DLPFC would likely manifest itself as the inability to delay gratification, resulting in steeper rates of discounting and lower working memory capacity.

Clinical Implications

The large overlapping cluster identified in the present analysis represents a new target site for therapies such as TMS or real-time fMRI neurofeedback. Its location in the posterior extent of the DLPFC and adjacent to the inferior frontal junction is ideally situated to influence executive processes. We hypothesize that this area is associated with integrating temporal information about the recent past and the foreseeable future into ongoing executive processes while making decisions. Future studies in our lab will directly test the ability of activity in this area to modulate performance on delay discounting and working memory tasks in healthy and addicted populations.

Considerations and Limitations

There are some facets to consider when interpreting the current findings. Each meta-analysis included pediatric-aged participants. Since these studies did not distinguish between data points obtained from pediatric subsamples and other individuals, it was not possible to exclude subjects less than 21 years of age. We took additional steps, however, to ensure our results were not due to age. First, ALE contrasts (set to thresholds used in the current analysis) between studies that included participants less than and greater than 21 years of age revealed no significant differences in brain maps (i.e., DD = 6 vs.12 studies, WM = 5 vs. 22 studies, FT = 9 vs. 26 studies, and RI = 15 vs. 13 studies). Second, an analysis of age across tasks revealed no significant differences $F_{3,93} = 2.28$, $p = .085$. The mean (±SE) reported ages were DD = 26.28 ± 1.6, WM = 33.48 ± 2.5, FT = 33.03 ± 2.7, and RI = 27.04 ± 2.3.

The current analyses were limited to studies examining whole-brain function in stereotactic space. While this facilitated matching studies and minimizing statistical bias, some studies were excluded on the basis of region of interest analyses (i.e., anatomical and/or functional). These studies, however, remain important and potentially contribute to a more informed understanding of the brain activity associated with the tasks examined. Imaging contrasts in the current study were obtained from experiments using a variety of statistical thresholds and correction procedures. Although this is consistent with the meta-analytical approach, our results represent a broad survey of the functional brain activity associated with the tasks examined. Finally, as the goal of the current analysis was to examine a unique functional relationship between delay discounting and working memory, task activity was removed during subtraction and overlap analyses. As such and from a neural network perspective, there are likely important dynamics associated with delay discounting and working memory that are not captured in the current work. Such dynamics may include temporal and spatial patterns of brain activity necessary for choosing future rewards by avoiding past mistakes.

To summarize, the current ALE analyses generated brain activity maps associated with performing tasks of delay discounting, working memory, finger tapping, and response inhibition. Maps of finger tapping and response inhibition were contrasted with maps of delay discounting and working memory to isolate a common temporal thread in executive ability. Overlap analyses revealed delay discounting and working memory share unique

function in the left lateral PFC. These data add to the previously observed behavioral relationship between delay discounting and working memory (11) by identifying a brain location where shared processes are likely to occur. This location represents a new therapeutic target for treatment strategies aimed at enhancing the ability to increase working memory processes and the value placed on future rewards.

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