(3) 就寝間近に熱いお風呂に入ることは避ける.
(4) 就寝1～2時間前より500ルクス以上の光環境を避ける.
(5) 眠れない場合には，無理に眠ろうとしない.

睡眠健康増進に関する研究で，ほぼ良好な結果の得られている事実を一日の生活習慣のなかに取り込み，とりまとめたものを図に示します．この図に示した生活習慣の調整法は高齢者を想定したものですが，若年者，中高年者でも原則はかわりません．毎日必ずすべてのものを行う必要はなく，可能なものから，週3回程度行っていくことで，快適な睡眠を確保するために有効な生活習慣を持続できます.

サーカディアンリズム（circadian rhythm）： 人間の生命現象は脳内視床下部の視交叉上核に存在する生物時計により，約24時間の周期で変動している．睡眠・覚醒リズムも生物時計の支配下にあり，サーカディアンリズムの不規則性が睡眠を悪化させる例も知られている.

悪化した睡眠は一朝一夕に改善できるものではありません．睡眠に関する知識が不十分な場合には，睡眠にとって有用な生活習慣を教示し，生活習慣の改善については，4～8週間の計画の中で，睡眠障害の症状の改善状態を評価しながら行うことが大切です.

特集
夜間頻尿

睡眠障害と夜間頻尿

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Key Words　睡眠障害，夜間頻尿，高齢者，妊産婦，QOL

睡眠障害は健康被害をもたらし，加齢とともにその発生率が増加する．日常生活を障害する長期不眠は，高齢者では15％以上と見込まれ，高齢者のQOLを阻害する重要な要因である．睡眠障害の原因として，睡眠機能の低下，サーカディアンリズムの異常，身体・精神・神経疾患，生活習慣などが指摘されているが，夜間頻尿に関してはこれまであまり注目されていない．また，高齢者以外にも夜間頻尿により睡眠が障害される場面は，妊娠末期や更年期でも頻発する．本文では，夜間頻尿と睡眠障害との関係について概説する．

I　睡眠と健康

睡眠障害の健康に対する被害について，近年急速に研究が進んできている．また，睡眠障害のみでなく睡眠時間の不足も，健康を障害する可能性が指摘されている．100万人以上を対象としたKripkeら[1)]のコホート研究の結果では，6時間30分未満あるいは8時間以上の睡眠時間の者では健康被害のリスクが有意に増大している．また，不眠患者の50％が，12カ月以内に睡眠障害以外の何らかの医療的治療にかかっていることも，WHOの国際共同研究[2)]で確認されている．

睡眠が障害された場合に生じる個々の健康被害についても，かなりよく研究されている．睡眠障害により，免疫機能は減弱し，生体防御や生体維持機能が低下[3)]すると考えられている．循環器機能には，さらに深刻な影響が生じる．睡眠時呼吸障害は，高血圧症，右心室肥大，不整脈，多血症などの原因となり，虚血性心疾患や脳血管性痴呆の重要な要因となることが指摘[4)]されている．

痴呆等と直接的に関連する認知機能と睡眠との関係も，近年研究が盛んである．睡眠障害や睡眠

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不足は，注意（attention）を強く障害することが，多くの報告[5-8]から明らかとなっている．また，眠気は脳内の情報処理過程にも影響を及ぼす．睡眠不足より脳内情報処理に対応して出現する事象関連電位の1つであるP300の潜時が延長し注意の指標である振幅が減少し[9]，睡眠時呼吸障害による夜間睡眠の分断が，覚醒時の前頭葉，側頭葉，頭頂葉において，注意機能の指標であるP300の振幅を減衰[10]させる．

特に高齢者では，睡眠の障害あるいは不足は，認知機能の悪化に強く影響している可能性が高い．Asadaらは，アルツハイマー型痴呆患者の発症の危険因子について疫学的に検討し，60分未満の昼寝習慣をもつ者は危険率が有意に低下することを報告[11]しており，睡眠習慣や睡眠障害とアルツハイマー型痴呆発症との間に何らかの関連のあることも推定されている．

睡眠障害や睡眠不足は，学習や記憶にも影響する．夜間睡眠が分断され日中に強い眠気の混入する睡眠時呼吸障害の患者では，記憶が障害されるとする報告[12]は多い．また，1,000名の米国民を対象としたランダムサンプリングによる調査で，対象者を短期不眠，長期不眠および非不眠に分類し日中の状態を比較した研究では，不眠者で記憶，集中力，課題遂行力や人間関係を楽しむ能力に障害がみられたことが報告[13]されている．また，睡眠障害と記憶の関係では，ベンゾジアゼピン系，非ベンゾジアゼピン系を問わず，睡眠導入剤の副作用として記憶障害の存在することがよく知られている[14]．睡眠の分断や不足はREM睡眠を減少させる．REM睡眠は，記憶の固定過程に関与している可能性が高く[15-18]，学習能力の衰退との関連も疑われている．

前頭連合野のより高次な脳機能と睡眠との関係は，若年者に36時間の断眠を行わせた場合に，短期記憶テストの正解に対する自信度や連想記憶の想起能力が，高齢者のスコアまで低下するとする報告[19]，高齢不眠では，社会に対する協調性の低下や自己の生活に関する満足度などの意欲が低下するという筆者らの報告[20]などがある．

21～75歳の男女212名を対象に，ピッツバーグ睡眠質問票（PSQI）[21]とSF-36[22]を用いて睡眠障害とQOLとの関係を検討した筆者らの結果を図1に示す．PSQIの11点以上は睡眠障害の疑いが高いと判断され，11点以上と11点未満の2群でQOLを比較した．SF-36によるQOLは，身体健康と精神健康のサマリースコアに類別され，両者ともPSQIが11点以上の睡眠障害の疑いのある群で有意に悪化していた．このように睡眠障害は，身体，精神両面の健康に関連したQOLを障害し，生活に支障をもたらす原因となる．

睡眠障害の治療として，睡眠薬の投与でことたれりとする治療方針は，認知機能への悪影響の面から考えれば誤りである．大多数の睡眠薬は，認知機能に何らかの悪影響を及ぼすとともに，長期にわたる服用は健康を障害する可能性も疑われている[1]．睡眠障害の治療場面では，必要に応じての睡眠薬の適切な投与とともに，認知・行動療法などの睡眠衛生あるいは生活習慣の調整技術が有用な場合が多い[23]．

Ⅱ　夜間頻尿と睡眠障害

夜間頻尿は，単に高齢者の問題ではない．図2は，558名の18～45歳の非妊娠，妊娠女性の夜間排尿回数を比較した結果である．この年齢層の非妊婦では，わずか3.1％の女性が夜間入眠後に2回以上排尿があるのに対して妊婦では妊娠初期で23.6％，妊娠中期で32.7％，妊娠末期で

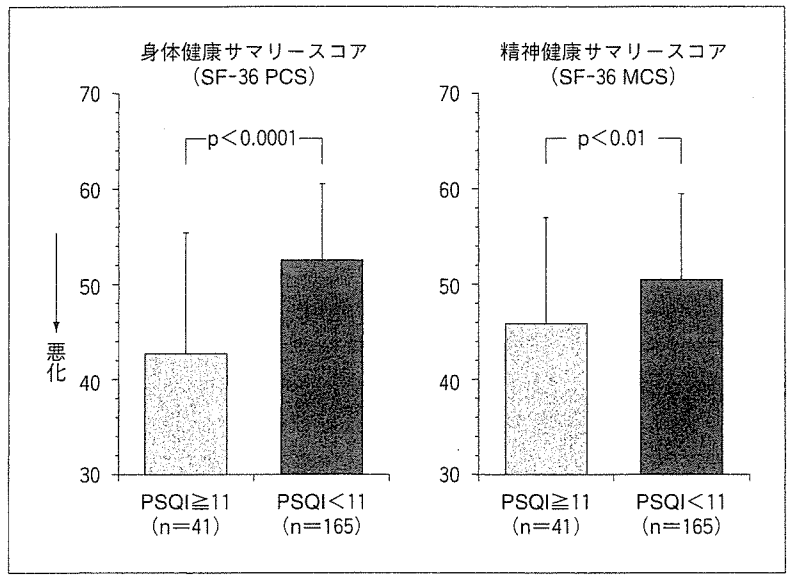

図1　睡眠障害による QOL の障害

ピッツバーグ睡眠質問票（PSQI）得点が 11 点以上の睡眠障害者では，SF-36 による身体健康と精神健康のサマリースコアが有意に悪化し QOL が障害されている．

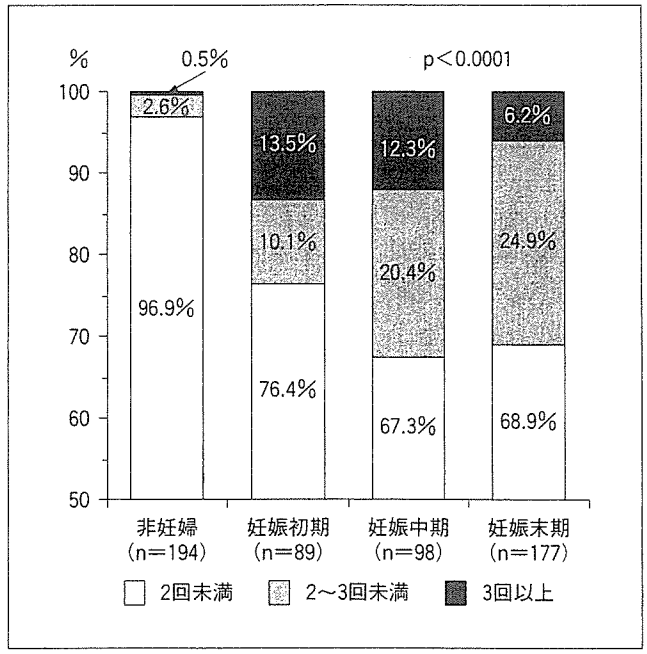

図2　非妊婦と妊婦における夜間排尿回数の差異

非妊婦に比べ妊婦では，夜間排尿回数の多い者が有意に妊娠初期から増加する．

31.1％と極端に増加する．妊娠初期でも明らかに高い夜間排尿回数を示し，この原因が胎児による膀胱の圧迫ではないことが明瞭である．体液循環量の増加，尿濃縮やナトリウム保持などの腎機能の変化，膀胱機能の変化，利尿ホルモンの分泌促進，抗利尿ホルモンのサーカディアンリズム異常などが考えられるが原因は不明である．この対象群での睡眠維持の障害は妊娠中期の群で最も強く，次いで末期，初期の順である[24]．このように妊婦においても夜間頻尿が睡眠障害に関係している可能性は高い．

東京圏の一般高齢住民192名を対象として，長期不眠の発症リスク検索を行った筆者らの調査[25]では，睡眠維持の障害に対する夜間頻尿の寄与率は0.447と思った以上に高く，高齢者に多い不適切な生活習慣を大きく上回っていた．疾患発症要因の検索で得られる値としては，これまで知られているものの中でも際だって高い値である．高齢者の場合，実質的な排尿の必要がない場合でも，夜間睡眠が障害され中途覚醒後に膀胱内圧が軽度でも高まっているとトイレに行くことが知られている．このような夜間頻尿は，睡眠障害が主たる原因であるが，排尿障害が中途覚醒の頻度を増大させることを自身が体験しているため，このような状況が生じやすい．中途覚醒後に，排尿に行かず再入眠する場合と，排尿に行き再入眠する場合では，行動覚醒による睡眠の中断，トイレでの光環境による覚醒効果，冬などは室温の低下による寒冷刺激など，再入眠を困難とする要因が，排尿行動には含まれている．このようなさまざまな要因の含まれる夜間頻尿が，高齢者の熟眠不全や中途覚醒を主訴とする長期不眠に関与している可能性は高い．

癌・循環器疾患の発症率が低く健康余命を誇る沖縄では，東京圏と比べ睡眠障害愁訴率は低いが，それでも高齢者の10％弱に長期不眠が認められた．筆者らが那覇市近郊で行った60～99歳の男女732名を対象とした睡眠健康に関する調査で，60歳代で7.1％，70歳代で9.9％，80歳以上では17.6％の者が1カ月以上持続する不眠を訴えていた．これらの長期不眠の多くは，入眠困難を主訴とするものでなく，中途覚醒等による睡眠維持の障害が主たる病像であった．

上記沖縄在住の高齢者での睡眠中の中途覚醒頻度と夜間排尿回数の関係を**図3左**に示す．**図3左**は，一カ月平均の夜間排尿回数と中途覚醒頻度との関係を散布図と回帰直線で示したものである．夜間頻尿のある高齢者は，明らかに中途覚醒が増加している．両者の相関は，$r = 0.7208$（$p < 0.0001$）と非常に高い．夜間排尿回数が3回未満の者の中途覚醒頻度のばらつきは大きいが，3回以上の夜間排尿回数を示す者では，中途覚醒頻度との関係がほぼ一線上に分布している．

一晩に2回未満，2回以上3回未満，3回以上の者の割合を，長期不眠者とそれ以外の者で**図3右**に示す．長期不眠者では，23.8％の者が3回以上の夜間睡眠中の排尿回数を示すのに対し，長期不眠をもたない者では8.8％であった．一般に，2回以上の中途覚醒が存在する者では不眠愁訴の多いことが，経験的に知られている．そこで2回以上の夜間排尿回数を示す者の割合を両群で比べてみると，長期不眠者では55.6％と半数以上であるが，長期不眠をもたない者では29.4％と両群には明らかな差（$p < 0.0001$）が認められている．この対象群では，性差や肥満度で夜間排尿回数に差は認められていない．また，長期不眠の発症頻度にも性差や肥満度で差は認められない．これらのことは，高齢者の長期不眠の発症に夜間頻尿が相当な比重を占めている可能性の高いことを示唆している．

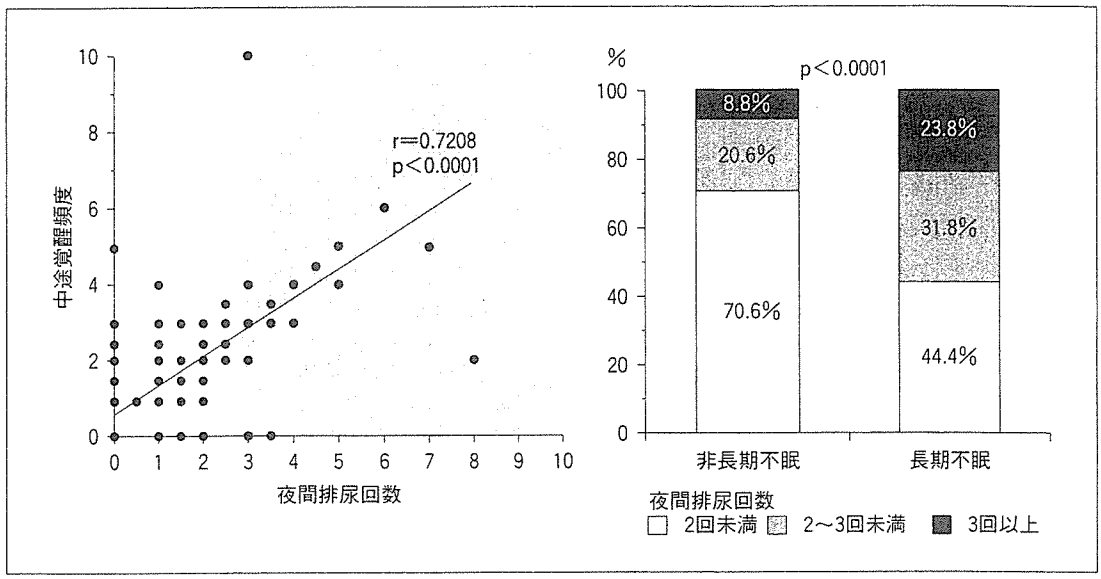

図3　夜間排尿回数と中途覚醒頻度との関係

沖縄在住男女732名（女性418名，男性314名，60～99歳）の夜間排尿回数と中途覚醒頻度との関係を図左に散布図で示す．夜間頻尿のある者では，明らかに中途覚醒が増加する．両者は，r = 0.7208と非常に高い相関を示す．図右に，長期不眠者と非長期不眠者での夜間排尿回数頻度の割合を示す．長期不眠愁訴をもつ者では，有意に夜間排尿回数が多い．

夜間排尿回数と中途覚醒頻度は，加齢とともに増加する．60歳代では，夜間排尿回数は平均で1.0回，中途覚醒は1.3回であるが，70歳代ではそれぞれ1.4回と1.5回に増える．さらに80歳を超えると夜間排尿回数は2.1回と平均で2回を超え，中途覚醒頻度も2.3回となっていた．特に問題となりやすい夜間排尿3回以上の者は，60歳代では約5％であるが70歳代で11％となり，80歳を超えると32％にもなる．同時に，長期不眠愁訴も7％，10％だったものが80歳を超えると18％にも増加していた．加齢とともに夜間排尿3回以上の者が増え，それに伴って長期不眠愁訴が増大し，両者の加齢による増加パターンは，相当に類似し高齢者では夜間頻尿が長期不眠を引き起こしている可能性が高い．

高齢者において長期不眠と夜間頻尿は，表裏一体の関係にあることが多い．睡眠が質的に悪化し中途覚醒が増えるので二次的に夜間頻尿となるケースも多々存在する．一方で，前立腺肥大のような泌尿器疾患により夜間頻尿が生じ，それが睡眠維持障害を引き起こす場合[26]もある．また，高齢者の2％以上に，腎透析患者では20～30％にみられるむずむず脚症候群[27]のような特異な睡眠障害が，夜間頻尿を併発している場合もある．さらに，抗利尿ホルモンの日内変動の異常が，サーカディアンリズム異常により引き起こされている症例も存在すると推定されている．さまざまな要因が夜間の排尿回数と排尿量を増加させ睡眠を障害するが，その多くは一日排尿量には差異はみられないとの報告[28]もあり，治療指針を策定するうえでも，日中と夜間の排尿量配分の検査は重要な指標となりうる．

中高年女性を対象とした調査であるが，運動習慣を有する女性では入眠後の排尿回数が少ないと

いう結果[29]が得られている．夜間頻尿の発症は，サーカディアンリズムを含めての生活習慣全般が関連している可能性が高く，適切な生活指導法の開発についても今後考慮する必要がある．

睡眠障害の治療の多くは，単に睡眠薬を投与することが多いが，泌尿器疾患が起因となっている睡眠障害，むずむず脚症候群のような特異な睡眠障害には効果のない場合が多い．これらが睡眠障害患者への睡眠薬の多剤投与や，常用量以上の多量の薬剤投与につながっている可能性は否定できない．高齢者の30％近くが，何らかの睡眠障害を発症している可能性が指摘されている現在，高齢者の睡眠障害治療において，エビデンスに基づく医療を提供することが望ましい．このような面からも，早急に高齢者の夜間頻尿の原因分類と治療指針の確立が期待される．

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RESEARCH ARTICLE

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Functional significance of delay-period activity of primate prefrontal neurons in relation to spatial working memory and reward/omission-of-reward expectancy

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Abstract The lateral prefrontal cortex (LPFC) is important in cognitive control. During the delay period of a working memory (WM) task, primate LPFC neurons show sustained activity that is related to retaining task-relevant cognitive information in WM. However, it has not yet been determined whether LPFC delay neurons are concerned exclusively with the cognitive control of WM task performance. Recent studies have indicated that LPFC neurons also show reward and/or omission-of-reward expectancy-related delay activity, while the functional relationship between WM-related and reward/omission-of-reward expectancy-related delay activity remains unclear. To clarify the functional significance of LPFC delay-period activity for WM task performance, and particularly the functional relationship between these two types of activity, we examined individual delay neurons in the primate LPFC during spatial WM (delayed response) and non-WM (reward–no-reward delayed reaction) tasks. We found significant interactions between these two types of delay activity. The majority of the reward expectancy-related neurons and the minority of the omission-of-reward expectancy-related neurons were involved in spatial WM processes. Spatial WM-related neurons were more likely to be involved in reward expectancy than in omission-of-reward expectancy. In addition, LPFC delay neurons observed during the delayed response task were not concerned exclusively with the cognitive control of task performance; some were related to reward/omission-of-reward expectancy but not to WM, and many showed more memory-related activity for preferred rewards than for less-desirable rewards. Since employing a more preferred reward induced better task performance in the monkeys, as well as enhanced WM-related neuronal activity in the LPFC, the principal function of the LPFC appears to be the integration of cognitive and motivational operations in guiding the organism to obtain a reward more effectively.

Keywords Delayed response · Monkey · Prefrontal cortex · Reward · Working memory

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Introduction

The lateral prefrontal cortex (LPFC) is thought to play its most important role in cognitive control (Fuster 1997; Miller and Cohen 2001), particularly in retaining and manipulating information in working memory (WM) (Goldman-Rakic 1996). LPFC-injured patients and monkeys with LPFC ablation show severe deficits in the learning and performance of WM tasks, including delayed response, delayed alternation and delayed matching to sample tasks (Jacobsen 1935; Mishkin 1957; Passingham 1975; Freedman and Oscar-Berman 1986). Human neuroimaging studies have demonstrated activation of the LPFC in association with WM task performance (D'Esposito et al. 1998; Owen et al. 1998). During the delay period of a WM task, primate LPFC neurons show sustained activity (Kubota and Niki 1971; Fuster 1973; Niki 1974; Kojima and Goldman-Rakic 1982; Quintana et al. 1988) and many show differential delay activity depending on differences in the spatial or object cues (Niki 1974; Quintana et al. 1988; Funahashi et al. 1989). Delay neurons with cue-related differential activity are thought to be involved in retaining task-relevant cognitive

information in WM, although the functional significance of delay neurons without cue-related differential activity remains unclear. Furthermore, it has not yet been determined whether delay neurons observed during WM tasks are concerned exclusively with the cognitive control of task performance.

Recently, delay-period activity that is not associated with WM has been reported in the monkey LPFC, particularly in LPFC delay neurons that are related to motivational operations, namely reward expectancy (Watanabe 1996; Leon and Shadlen 1999; Roesch and Olson 2003) and omission-of-reward expectancy (that is, anticipation of no-reward as the trial outcome during the reward–no-reward delayed reaction task) (Watanabe et al. 2002). These neurons show a differential delay activity between reward and no-reward trials, and/or among trials in which different types of reward might or might not be expected.

We reported previously that LPFC delay neurons showed both spatial WM-related and reward expectancy-related activities during a delayed response task using several different types of reward (Watanabe 1996). In an oculomotor delayed response task with both reward-present and reward-absent conditions, Kobayashi et al. (2002) reported both spatial WM-related and reward/omission-of-reward expectancy-related LPFC neurons. However, the functional relationship between the reward/omission-of-reward expectancy-related and spatial WM-related neuronal activities remains unclear. In order to clarify the functional significance of delay-period activity for WM task performance, and particularly the functional relationship between these two types of delay-period activity, we examined individual LPFC delay neurons during both WM and non-WM tasks; that is, spatial-memory (spatial delayed response) and outcome-expectancy (reward–no-reward delayed reaction) tasks. In addition, we examined whether neurons that showed delay (either differential or non-differential) activity in one type of task also showed delay (particularly differential delay) activity in the other. Furthermore, we examined individual LPFC delay neurons during both types of task in relation to their spatial and reward discrimination.

We postulated that not all delay neurons observed during the spatial-memory task would be concerned with the cognitive control of WM task performance, as delay-period activity was also observed during a non-WM task in the monkey LPFC (Watanabe et al. 2002). We further suggested that there would be some associations between WM-related and reward/omission-of-reward expectancy-related activities, as monkeys perform the WM task to obtain a reward and are reluctant to perform the task when no reward is expected. We made the following specific predictions: first, that more reward-expectancy than omission-of-reward expectancy neurons would show delay-period activity and would be concerned with retaining spatial information in WM during the spatial-memory task; second, that the majority of omission-of-reward expectancy neurons would not be involved in retaining information in WM; and third, that WM-related neurons would be more concerned with reward expectancy than with omission-of-reward expectancy.

We found that the majority of reward-expectancy neurons and the minority of omission-of-reward expectancy neurons were involved in spatial WM processes. We also discovered that spatial WM neurons were more likely to be involved in reward expectancy than in omission-of-reward expectancy. In addition, the data indicated that not all delay neurons observed during the spatial-memory task were concerned directly with the cognitive control of WM task performance.

Materials and methods

Subjects and behavioral training

Three male Japanese monkeys (*Macaca fuscata*) weighing 5.5–6.5 kg were used in this study. The monkeys were trained on an outcome-expectancy (reward–no-reward delayed reaction) task and a spatial-memory (spatial delayed response) task. Each monkey faced a panel that was positioned 33 cm away at eye level. The panel displayed three horizontally arranged rectangular windows (6×7.5 cm), three horizontally arranged circular keys (diameter = 5 cm) and a holding lever (width = 5 cm, protrusion = 5 cm) (Fig. 1a). The distance between adjacent rectangular windows, and between adjacent circular keys, was 10 cm from center to center. The distance between each rectangular window and the circular key immediately below it was 8 cm from center to center. Each window contained one opaque screen and one transparent screen with thin vertical lines. In the outcome-expectancy task, only the center window, center key and holding lever were used. In the spatial-memory task, the two windows on the left and right, the two keys on the left and right, and the holding lever were used.

outcome-expectancy task

There were three versions of this task: visible food, cued food and cued liquid. In the visible-food version (Fig. 1b), the monkey initially depressed the lever for 10–12 s (Pre-inst). The opaque screen of the window was then raised to reveal a food tray, either with (reward trial) or without (no-reward trial) a reward behind a transparent screen, for a 1-s duration as an instruction (Inst). After a delay of 5 s (Delay), a white light appeared on the key as a go signal (Go signal). When the monkey released the hold lever and pressed the key within 2 s after the go signal, both screens were raised and the monkey either collected the food reward (reward trials) or went unrewarded (no-reward trials), depending on the trial type. Reward and no-reward trials were alternated pseudo-randomly at a ratio of 3:2. Even in no-reward trials, the monkey had to press the key in order to advance to the next trial. In other versions of the outcome-expectancy task, a 1-s long color instruc-

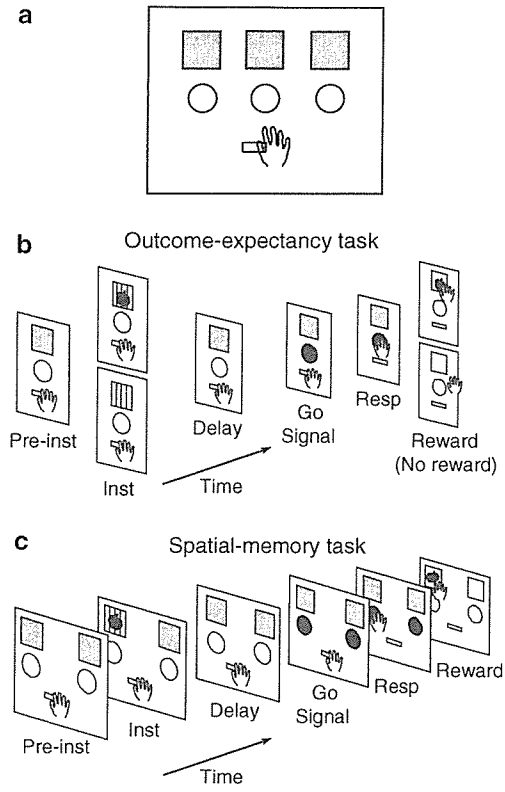

Fig. 1 The experimental panel and sequence of events used in the two types of task. **a** The experimental panel contained three horizontally arranged windows, three horizontally arranged keys and a holding lever. **b** The sequence of events in the visible-food version of the outcome-expectancy task. For brevity, only the center window, center key and holding lever are illustrated. The *upper panel* represents the reward trials and the *lower panel* represents the no-reward trials. *Inst* Instruction, *Resp* Response. **c** The sequence of events in the visible-food version of the spatial-memory task. For brevity, only the two (*left* and *right*) windows, two keys and holding lever are illustrated

tion (red or green) on the key indicated whether a reward would be delivered: red indicated reward trials and green indicated no-reward trials. In the cued-food version, depending on the instruction, a food reward could be collected (reward trials) or not collected (no-reward trials) behind the screens at the end of the trial. In the cued-liquid version, a drop of liquid was delivered (reward trials) or not delivered (no-reward trials) through a tube positioned close to the mouth of the monkey. Pieces (about 0.5 g) of raisin, sweet potato, cabbage or apple were used as food rewards. Drops (0.3 ml) of water, sweet isotonic beverage, orange juice or grape juice were used as liquid rewards. The same reward was used continuously for a block of about 50 trials; it was assumed that the animal knew, which reward was being used in each block after two or three trials. Each instruction stimulus was thus associated with the presence or absence of a particular kind of reward. The monkeys were not required to perform any differential operant action related to differences between the rewards. In the food-reward tasks, both windows were closed when the monkey returned its hand to the holding lever after the key press. The trial was aborted if the monkey released the hold lever before the go signal.

spatial-memory task

There were three versions of this task: visible food, cued food and cued liquid. In the visible-food version (Fig. 1c), the monkey initially depressed the lever for 10–12 s (Pre-inst). The opaque screen of the left or right window was then raised to reveal a food tray behind a transparent screen for a 1-s duration as an instruction (Inst). After a delay of 5 s (Delay), a white light appeared on the left and right keys as a go signal (Go signal). When the monkey released the hold lever and correctly pressed the key on the indicated side within 2 s after the go signal, the left and right screens were raised and the monkey could collect the food reward. When the monkey did not respond to the correct side, the trial ended without the window opening. In the cued-food and cued-liquid versions of the spatial-memory task, a red light was presented on the left or right key for a 1-s duration to indicate the correct side for the response. After a delay of 5 s, a go signal of white light appeared on both keys, and the monkey was required to touch the key on the cued side within 2 s after the go signal. Correct responses were rewarded with the food or liquid. The rewards and methods of reward delivery used during the spatial-memory task were the same as those used in the outcome-expectancy task. The same reward was used continuously for a block of about 50 trials.

The task was controlled using a personal computer (NEC, PC9801FA, Tokyo). No attempt was made to restrict the eye movements of the animals. On weekdays, the monkeys received their daily liquid requirement while performing the task. Water was available ad libitum during weekends. Monkey pellets were available ad libitum in the home cage at all times, while more preferred foods were used as rewards in the laboratory experiments.

Reward-preference tests

The reward preferences of each monkey were assessed in separate blocks of choice trials before or after the behavioral testing of each animal. Preferences for different foods were assessed in free-choice tests by simultaneously presenting several items to the monkey. Preferences for different reward liquids were assessed by testing the willingness of each monkey to perform the task with one liquid after it had refused to perform the task with another.

Surgery and recording

Details of the procedure are described elsewhere (Watanabe et al. 2002). Briefly, on completion of training, each monkey was surgically prepared under sodium pentobarbital anesthesia (Nembutal; 30 mg/kg).

A stainless steel cylinder (diameter, 18 mm) was implanted as a microdrive receptacle at appropriate locations on the skull. A hollow rod (diameter, 15 mm) for head fixation was attached to the skull using dental acrylic. During recording sessions, the head of the animal was fixed rigidly to the frame of the monkey chair using the head holder, and a hydraulic microdrive (MO95-C; Narishige, Tokyo) was attached to the implanted cylinder. Elgiloy electrodes (Suzuki and Azuma 1976) were used for the neuronal recordings. Neuronal activity was recorded from both the banks and lips of the principal sulcus, the inferior convexity and the arcuate areas of the LPFC of both hemispheres of the three monkeys. The action potentials were passed through a window discriminator and converted into square-wave pulses. During the recordings, we changed the task approximately every 50 trials between the outcome-expectancy and spatial-memory tasks, and/or the task version and/or the type of reward. We monitored the position and movement of the eyes of the animals using an infrared eye-camera system (R-21C-A; RMS, Hirosaki, Japan; sampling rate = 4 ms) during the task performance after neuronal recording had been completed.

Data analysis

Impulse data were displayed as raster displays and frequency histograms. Non-parametric statistics were used for the analysis. Data from the first few trials after changing the task and/or type of reward were omitted from the analysis. Initially, the magnitudes of neuronal activity in relation to the task events (pre-instruction, instruction presentation, delay, go signal, key-press response, reward delivery and omission of reward) were compared with the control activity (2–3 s before the instruction) within the same reward block of trials, separately for reward and no-reward trials in the outcome-expectancy task, and for left and right trials in the spatial-memory task, using the Mann–Whitney *U*-test. The criterion for statistical significance was set at $P < 0.05$ (two-tailed). The magnitude of neuronal activity in relation to each task event was compared between reward and no-reward trials in the outcome-expectancy task and between left and right trials in the spatial-memory task using the *U*-test. Different reward blocks were compared using the Kruskal–Wallis *H*-test. The *U*-test was used for post hoc analysis when a statistically significant difference was observed using the *H*-test. Reaction time (RT) data (that is, the time between the presentation of the go-signal and the key-press response by the monkey) were also examined using non-parametric *U* and *H* tests. In addition, we used the χ^2 and Fisher's exact probability tests to examine the frequency distribution. All of the experiments were conducted in accordance with the NIH Guidelines for the Care and Use of Laboratory Animals (1996) and were approved by the ethics committee of the Tokyo Metropolitan Institute for Neuroscience.

Results

Behavioral results

Among the food rewards, preference tests demonstrated that the monkeys consistently preferred cabbage and apple to potato to raisin (>95% in free-choice tests). There was no significant difference in the preference between cabbage and apple. Among the liquid rewards, the monkeys invariably preferred grape juice, orange juice and isotonic beverage to water, and preferred grape juice to orange juice and isotonic beverage. The RTs were significantly influenced by the reward used in each trial. Details of the RT data are described elsewhere (Watanabe et al. 2001). For all rewards, the RTs were significantly shorter in reward trials than in no-reward trials. The RTs were shorter when a highly preferred reward was used compared with a less preferred reward, in reward and/or no-reward trials. During the neuronal recording sessions, the monkeys performed both tasks with >98% correct responses for all types of reward.

The eye-movement recordings revealed no significant difference in the frequency of saccadic eye movements between reward and no-reward trials in the outcome-expectancy task, between the left and right trials in the spatial-memory task, or between the different types of reward block. In addition, there was no significant difference between the left and right trials in the time spent looking at the left and right sides of the visual field during the delay period of the spatial-memory task.

Reward/omission-of-reward expectancy-related and spatial WM-related prefrontal neurons

Some of the findings regarding LPFC neuronal activity within each of the outcome-expectancy and spatial-memory tasks were reported previously (Watanabe 1996; Watanabe et al. 2002). The present report concerns 222 task-related neurons that were examined during both tasks. These showed significant activity changes compared to the control period (2–3 s before the instruction presentation) in relation to one or more task events (pre-instruction, instruction presentation, delay, go signal, key-press response, reward delivery and omission of reward) during at least one version of either task. Of these 222 neurons, we focus here on the 126 that could be examined for the same reward(s) in the same version (visible food, cued food or cued liquid) of both the outcome-expectancy and spatial-memory tasks (Table 1). The majority ($n = 113$; 89.7%) of these 126 task-related neurons showed delay-period activity; that is, they showed significantly higher or lower firing during the delay period compared with the pre-cue control period during both tasks (83 neurons), during the outcome-expectancy task alone (11 neurons) or during the spatial-memory task alone (19 neurons). Most of these 113 delay neurons ($n = 104$; 92.0%) showed differential activity depending on the trial type (reward

Table 1 Classification of LPFC neurons according to activity on the outcome-expectancy and spatial-memory tasks

Activity during the outcome-expectancy task	Activity during the spatial-memory task			Total
	Spatial-WM	Nondirectional-delay	Non-delay	
1 Reward-expectancy	35	11	0	46
2 Omission-expectancy	11	11	10	31
3 Outcome-unselective delay	13	3	1	17
4 Non-delay	14	5	13	32
Total	72	30	24	126

versus no-reward or left versus right) during both tasks (45 neurons), during the outcome-expectancy task alone (32 neurons) or during the spatial-memory task alone (27 neurons).

During the outcome-expectancy task, 77 of the 126 neurons showed outcome-selective delay activity; that is, they showed *significant* differences in the rate of firing during the delay period between reward and no-reward trials. Among these 77 neurons, 46 showed a significantly higher rate of firing in reward trials and 31 showed a significantly higher rate of firing in no-reward trials; the former were designated as "reward-expectancy" neurons and the latter as "omission-expectancy" neurons. Of the remaining 49 neurons, 17 showed delay-period activity without significant differences in activity between the reward and no-reward trials, and 32 showed no significant delay-period activity in both the reward and no-reward trials; the former, which showed non-differential delay activity, were designated as "outcome-unselective delay" neurons (Table 1).

In the spatial-memory task, 72 of the 126 neurons showed *significant* differences in delay activity between the left and right trials: 32 had a significantly higher rate of firing in the left trials and 40 had a significantly higher rate of firing in the right trials. These spatially differential delay neurons were designated as "spatial-WM" neurons. Of the remaining 54 neurons, 30 showed delay-period activity without significant differences in activity between the left and right trials, and 24 failed to show significant delay-period activity in either the left or the right trials; the former neurons, which showed non-differential delay activity, were designated as "non-directional delay" neurons (Table 1). The Pearson χ^2 -test revealed a significant association between the type of activity observed in the outcome-expectancy task and that observed in the spatial-memory task [$\chi^2 = 32.3$, degrees of freedom (df) = 6, $P < 0.001$; Table 1]. We also used the Fisher's exact probability test, which confirmed that the distribution in Table 1 was not a product of chance ($P < 0.001$).

As the activity of the reward/omission-expectancy neurons and the RTs of the monkeys were both related to the presence or absence of a reward, and to the type of reward, we thought that the activity of reward/omission-expectancy neurons might reflect the RT, that is, a larger magnitude of activity change in reward-expectancy neurons might induce a shorter RT in the response of the monkey. However, significant correlations between the magnitude of neuronal activity and the RT were found in most reward/omission-expectancy neurons during certain (for example, cabbage and potato, but not raisin) reward blocks, only when data from the reward and no-reward trials were combined. Regardless of the reward used, when a trial-by-trial correlation coefficient was calculated between the two measures within the reward or no-reward trials, there was no significant correlation ($P > 0.05$) between the two measures, and it was not possible to predict the RT in each trial from the magnitude of the activity in the reward/omission-expectancy neurons. Thus, RT was not directly associated with neuronal activity in the LPFC.

Eye movements were recorded separately from the neuronal data, so direct correlations could not be made between eye movements and LPFC neuronal activity. However, as there were no significant differences in eye movements and position between the different trial types during either the outcome-expectancy or spatial-memory tasks, it appeared that the differential delay activity observed in the LPFC neurons was not directly associated with eye movement or position.

Activity of reward-expectancy neurons during the spatial-memory task

All of the reward-expectancy neurons ($n = 46$) in the outcome-expectancy task showed delay-period activity during the spatial-memory task, with the majority ($n = 35$) showing spatial-WM activity: 17 neurons had a significantly higher rate of firing in the left trials than in the right trials (Fig. 2a), while 18 had a significantly higher rate of firing in the right trials (Fig. 2b). Twelve of the 35 neurons with both reward-expectancy and spatial-WM activity showed delay-period activity in either the left or right trial alone during the spatial-memory task (Fig. 3a). Of the 46 reward-expectancy neurons, 11 showed the same level of delay-period activity during the spatial-memory task and were non-selective for the remembered locations (Fig. 3b).

Activity of omission-expectancy neurons during the spatial-memory task

Almost one-third of the 31 omission-expectancy neurons ($n = 10$) showed no delay-period activity change

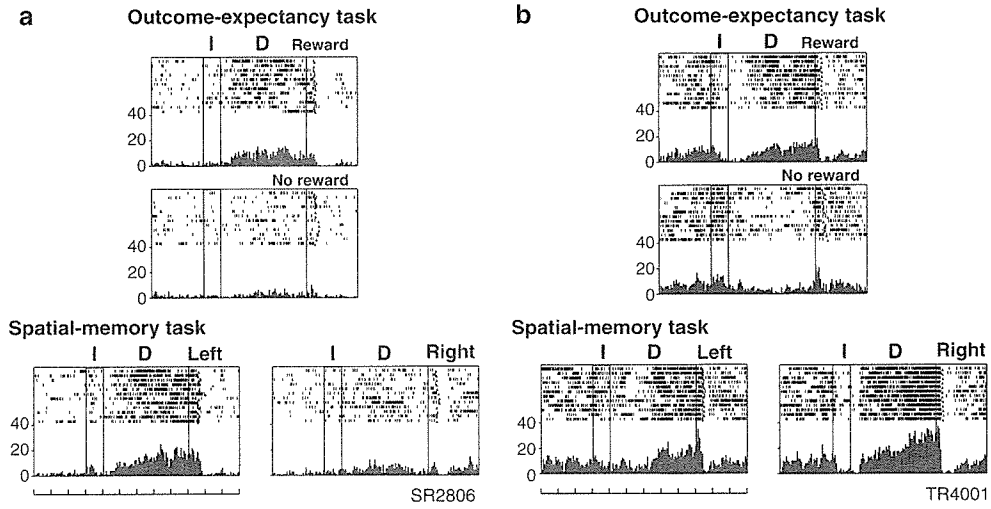

Fig. 2 Examples of reward-expectancy neurons showing spatial-WM activity during the spatial-memory task. **a** A neuron that was examined in the cued-food version of both types of task with the cabbage reward. This neuron showed reward-expectancy activity by exhibiting significant activations in the reward, but not the no-reward, trials during the outcome-expectancy task. During the spatial-memory task, this neuron showed spatial-WM activity by exhibiting a higher firing rate in the left trials than in the right trials. **b** A neuron that was examined in the visible-food version of both types of task with the cabbage reward. This neuron showed reward-expectancy activity by exhibiting significant activations in the reward, but not the no-reward, trials during the outcome-expectancy task. During the spatial-memory task, this neuron showed spatial-WM activity by exhibiting a higher firing rate in the right trials than in the left trials. For both **a** and **b**, neuronal activity is shown separately for the outcome-expectancy task (*upper part*) and the spatial-memory task (*lower part*) in raster and histogram displays. For the outcome-expectancy task, the *upper* and *lower panels* show neuronal activity for the reward and no-reward trials, respectively. For the spatial-memory task, the *left* and *right displays* show neuronal activity for the left and right trials, respectively. For each display, the first two vertical lines from the *left* indicate the instruction onset and offset, and the *third line* indicates the end of the delay period. *Each row* indicates one trial, and the small upward triangles in the *raster* indicate the time of the key-pressing responses. The *leftmost scales* indicate the number of impulses per second, and the time scale at the *bottom* indicates intervals of 1 s. *I* instruction, *D* delay, *Reward* reward trials, *No reward* no-reward trials, *Left* left trials, *Right* right trials. The *neuron numbers* (SR2806 and TR4001) are indicated on the bottom right

(Fig. 4a), and a similar number ($n=11$) showed non-directional delay activity during the spatial-memory task. Only 10 of the 31 omission-expectancy neurons showed spatial-WM activity during the spatial-memory task: three of these showed a significantly higher rate of firing in the left trials (Fig. 4b), while seven showed a significantly higher rate of firing in the right trials.

Activity of outcome-unselective delay neurons during the spatial-memory task

Of the 126 neurons that were examined in the outcome-expectancy task, 17 showed outcome-unselective delay activity: the majority of these ($n=13$) showed spatial-WM activity (Fig. 5a), three neurons showed non-directional delay activity (Fig. 5b), and one neuron showed no delay-period activity, during the spatial-memory task.

Activity of spatial-WM neurons during the outcome-expectancy task

We also examined whether spatial-WM neurons discriminated between reward and no-reward trials during the outcome-expectancy task. Of the 72 spatial-WM neurons, 45 discriminated between them: 35 of these showed reward-expectancy activity (Fig. 2a) and ten showed omission-expectancy activity (Fig. 4b) (Table 1). The remaining 27 neurons did not discriminate between reward and no-reward trials: 13 of these showed outcome-unselective delay activity (Fig. 5a) and 14 showed no delay-period activity.

Of the 30 non-directional delay neurons, 11 showed reward-expectancy activity (Fig. 3b), 11 showed omission-expectancy activity and three showed outcome-unselective delay activity (Fig. 5b) during the outcome-expectancy task (Table 1). Among the 24 neurons that did not show delay-period activity during the spatial-memory task, none showed reward-expectancy activity, ten showed omission-expectancy activity, one showed outcome-unselective delay activity and 13 showed no delay-period activity during the outcome-expectancy task (Table 1).

Spatial selectivity of delay neurons across the outcome-expectancy and spatial-memory tasks

Each monkey performed the outcome-expectancy and spatial-memory tasks separately. The left and right keys were used simultaneously during the spatial-memory task, while only the center key was used during the

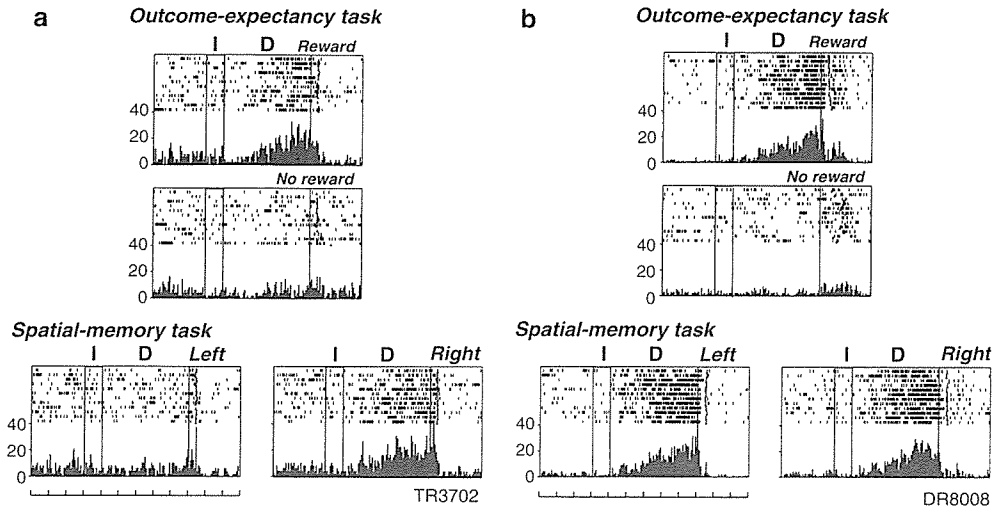

Fig. 3 Examples of reward-expectancy neurons showing spatial-WM (**a**) and non-directional delay (**b**) activity during the spatial-memory task. **a** A neuron that was examined in the cued-liquid version of both types of task with the water reward. This neuron showed reward-expectancy activity by exhibiting activations during the delay period only in the reward, and not the no-reward, trials during the outcome-expectancy task. During the spatial-memory task, this neuron showed spatial-WM activity by exhibiting activations only in the *right*, and not the *left*, trials. **b** A neuron that was examined in the cued-liquid version of both types of task with the orange juice reward. This neuron showed reward-expectancy activity by exhibiting activations only in the reward, and not the no-reward, trials during the delay period of the outcome-expectancy task. During the spatial-memory task, this neuron showed non-directional delay activity by exhibiting significant activations in both the *left* and the *right* trials, with no significant difference in the magnitude of activation. The other details are as described for Fig. 2

outcome-expectancy task. However, because previous reports have demonstrated that many LPFC delay neurons are involved in spatial mapping (for example, Funahashi et al. 1989), we examined whether there was any relationship between the delay activity observed in the rewarded center key trial in the outcome-expectancy task and that observed in the rewarded left and right trials in the spatial-memory task, using the 72 spatial-WM neurons.

The *H*-test indicated that all of the 72 spatial-WM neurons showed statistically significant differences in delay activity among the right, center and left trials ($P < 0.05$). The post hoc *U*-test demonstrated that in the majority (66 out of 72; 92%) of these neurons, the magnitude of the delay-period firing observed in the center key trials was not significantly larger than the maximum, nor smaller than the minimum, detected between the left and right key trials during the spatial-memory task. In 20 of these 66 neurons, significant differences were observed in the magnitude of delay-period firing both between the center and left key trials, and between the center and right key trials (Fig. 2a). In the remaining 46 neurons, significant differences in the magnitude of delay-period firing were observed either between the center and left key trials or between the center and right key trials (Fig. 3a, 4b). A small number of neurons (6 out of 72; 8%) showed a higher or lower rate of delay-period firing during the outcome-expectancy task than during the spatial-memory task (Fig. 2b, 5a). These neurons showed significant differences in the pre-instruction baseline activity between the outcome-expectancy and spatial-memory tasks.

Reward–no-reward-discrimination and left–right-discrimination in LPFC delay neurons

Because there were differences in the ability of each LPFC delay neuron to discriminate between the reward and no-reward trials and between the left and right trials, we compared the ability of individual LPFC neurons to discriminate reward/no-reward trials with their ability to discriminate left/right trials. We calculated the "reward–no-reward discrimination index" (RNRDI) of individual neurons using the following formula:

$$\text{RNRDI} = (\text{reward} - \text{no - reward})/(\text{reward} + \text{no - reward})$$

Here, "reward" and "no-reward" indicate the mean discharge rate during the delay period for the reward and no-reward trials in the outcome-expectancy task, respectively. Similarly, we calculated the "left–right discrimination index" (LRDI) of individual neurons using the following formula:

$$\text{LRDI} = (\text{left} - \text{right})/(\text{left} + \text{right})$$

Here, "left" and "right" indicate the mean discharge rate during the delay period for the left and right trials in the spatial-memory task, respectively. Both indices ranged between −1 and 1, with a larger absolute value indicating greater discrimination between the reward and no-reward trials (RNRDI), or greater discrimination between the left and right trials (LRDI). For those neurons that were examined using more than two different types of reward for both tasks, the mean values of

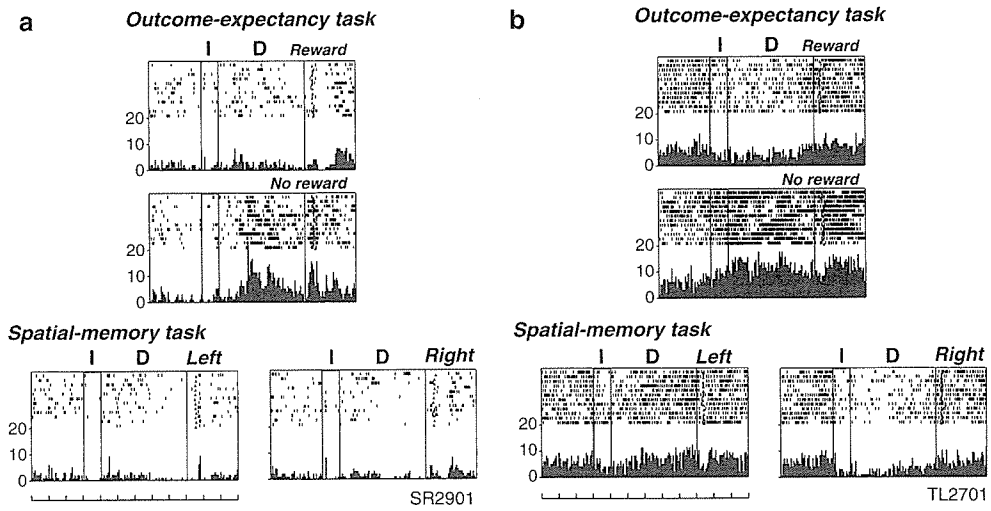

Fig. 4 Examples of omission-expectancy neurons without (**a**) or with (**b**) spatial-WM activity during the spatial-memory task. **a** A neuron that was examined in the visible-food version of both types of task with the raisin reward. This neuron showed omission-expectancy activity by exhibiting a higher firing rate in the no-reward trials than in the reward trials during the outcome-expectancy task. During the spatial-memory task, this neuron did not show significant delay-period activity. **b** A neuron that was examined in the visible-food version of both types of task with the cabbage reward. This neuron showed omission-expectancy activity by exhibiting a higher firing rate in the no-reward trials than in the reward trials during the delay period of the outcome-expectancy task. During the spatial-memory task, this neuron showed spatial-WM activity by exhibiting a higher firing rate in the *left* trials than in the *right* trials. The other details are as described for Fig. 2

the RNRDI and LRDI were obtained for the different types of reward for each neuron.

The mean (±SD) absolute RNRDI of the 77 (reward-expectancy plus omission-expectancy) neurons was 0.3114 (±0.1651) [0.30 (± 0.16) for the reward-expectancy neurons and −0.33 (±0.16) for the omission-expectancy neurons]. The mean absolute LRDI of the 72 spatial-WM neurons was 0.2833 (±0.1431). There was no significant difference between these two values ($P=0.2711$, two-tailed t-test). We also obtained the mean absolute values of the RNRDI and LRDI for the 45 delay neurons that showed both reward-expectancy (or omission-expectancy) and spatial-WM activity. The mean absolute RNRDI and LRDI values of these 45 neurons were 0.2980 (±0.1491) and 0.2547 (±0.1025), respectively. There was no significant difference between these two values ($P=0.115$, two-tailed t-test), although there was a weak, but statistically significant, correlation between these two indices ($r=0.4322$, $P<0.01$, two-tailed t-test) (Fig. 6). Thus, the greater the discrimination shown by a specific delay neuron between the reward and no-reward trials, the more it tended to discriminate between the left and right trials.

Comparison of reward discrimination by LPFC delay neurons between the outcome-expectancy and spatial-memory tasks

We reported previously on the ability of individual LPFC delay neurons to discriminate between different types of reward in the outcome-expectancy task (Watanabe et al. 2002). We compared the ability of individual LPFC delay neurons to discriminate between different types of reward during the outcome-expectancy task with that during the spatial-memory task. The "reward difference discrimination index" (RDDI) of individual neurons was calculated separately for reward trials in the outcome-expectancy task, and for combined left and right trials in the spatial-memory task, using the following formula:

$$\mathrm{RDDI} = (\text{preferred} - \text{non-preferred})/(\text{preferred} + \text{non-preferred})$$

Here, "preferred" and "non-preferred" indicate the mean discharge rate during the delay period for the most and least preferred rewards within a task, respectively. This index was calculated using data obtained from 26 neurons that were examined for the most (cabbage or grape juice) and least (raisin or water) preferred rewards in both the outcome-expectancy and spatial-memory tasks. This index also ranged between −1 and 1, with a larger absolute value indicating greater discrimination between the most preferred and least preferred rewards within a task. The mean absolute values of the RDDI were 0.1650 (±0.1041) in the outcome-expectancy task and 0.1478 (±0.1292) in the spatial-memory task. There was no significant difference between these two values ($P=0.6076$, two-tailed t-test), although there was a significant correlation between the two values ($r=0.6059$, $P<0.01$, two-tailed t-test) (Fig. 7), indicating that reward discrimination by LPFC delay neurons did not differ between the outcome-expectancy and spatial-memory tasks.

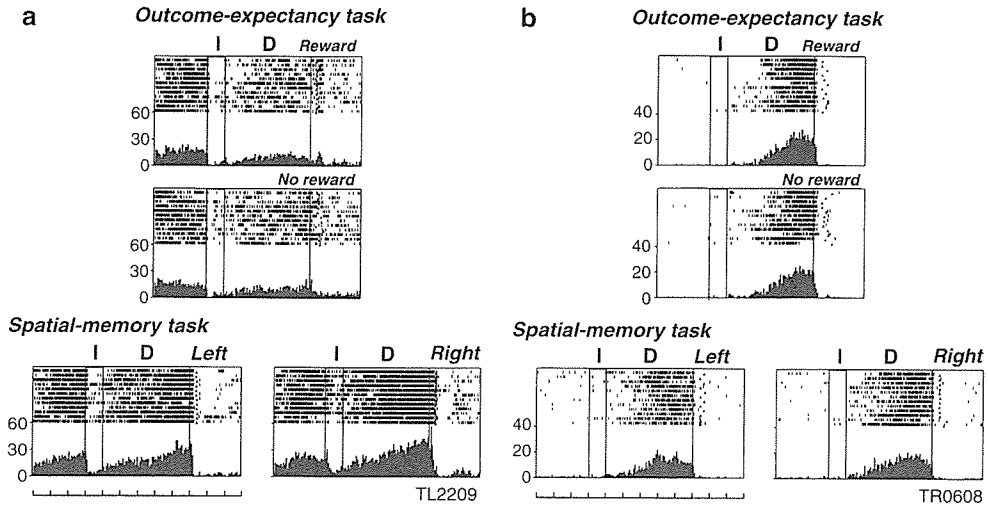

Fig. 5 Examples of outcome-unselective delay neurons with (**a**) and without (**b**) spatial-WM activity during the spatial-memory task. **a** A neuron that was examined in the visible-food version of both types of task with the potato reward. This neuron showed outcome-unselective delay activity by exhibiting a significant decrease in the firing rate during the delay period of the outcome-expectancy task, with no significant difference in activity between the reward and no-reward trials. During the spatial-memory task, this neuron showed spatial-WM activity by exhibiting a higher firing rate in the right trials than in the left trials. **b** A neuron that was examined in the cued-liquid version of both types of task with the water reward. This neuron showed outcome-unselective delay activity by exhibiting significant activations during the outcome-expectancy task, with no significant difference in activity between the reward and no-reward trials. During the spatial-memory task, this neuron showed non-directional delay activity by exhibiting activations in both the *left* and *right* trials, with no significant difference in activity between the *left* and *right* trials. The other details are as described for Fig. 2

Modulation of spatial-WM activity by reward-expectancy in LPFC delay neurons

We examined whether there was any enhancement in the ability to discriminate between the left and right trials in spatial-WM neurons when the more preferred reward was used in the spatial-memory task compared with the less preferred reward. We calculated the LRDI for all 21 spatial-WM neurons that were examined using both the most and least preferred rewards. The mean absolute value of the LRDI in these 21 neurons for the most preferred reward was 0.2810 (±0.1270), while that for the least preferred reward was 0.2610 (±0.1132). There was no significant difference in the absolute value of the LRDI between the most and least preferred rewards ($P=0.59$, two-tailed t-test). However, more than one-half of these spatial-WM neurons ($n=13$) showed a significantly higher rate of firing throughout the trial

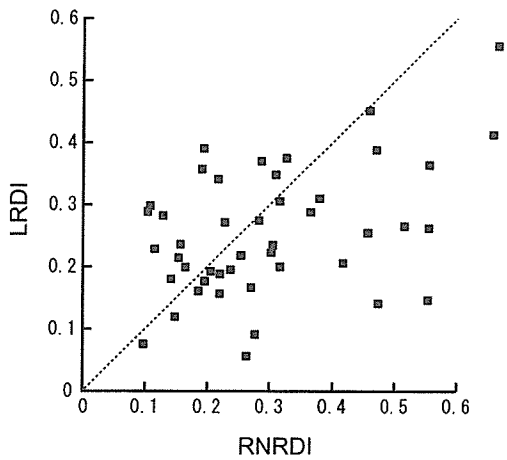

Fig. 6 Ability of LPFC delay neurons to discriminate between reward and no-reward trials (*RNRDI*) during the outcome-expectancy task, and between left and right trials (*LRDI*) during the spatial-memory task. Absolute values of the left–right discrimination index (*LRDI*) of individual LPFC neurons are plotted against those of the reward–no-reward discrimination index (*RNRDI*). Each filled square represents an individual LPFC neuron. The *dashed line* indicates 45°

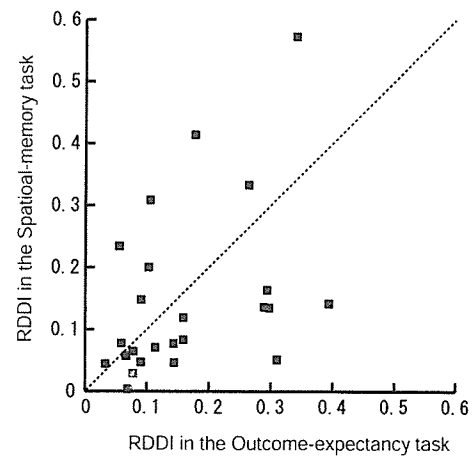

Fig. 7 Ability of LPFC delay neurons to discriminate between the most and least preferred reward blocks (*RDDI*) in the outcome-expectancy and spatial-memory tasks. Absolute values of RDDI in the spatial-memory task are plotted against those in the outcome-expectancy task. The other details are as described for Fig. 6

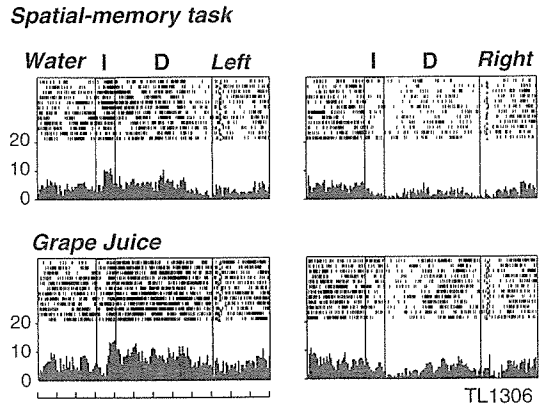

Fig. 8 An example of a spatial-WM (and reward-expectancy) neuron that discriminated between the most (grape juice) and least (water) preferred rewards. Although this neuron showed a higher rate of firing for the most preferred reward than for the least preferred reward during the delay period, there was no significant difference in left–right discrimination (*LRDI*) between the two different reward trials. The *upper* and *lower panels* correspond to the water and grape juice rewards, respectively. The other details are as described for Fig. 2

when the most preferred reward was used compared with the least preferred reward (Fig. 8). Thus, the use of the more preferred reward often induced an enhancement of the basal neuronal activity, but did not result in an improvement of spatial discrimination by spatial-WM neurons.

Location of reward/omission-expectancy and spatial-WM neurons in the LPFC

The locations of penetrations of the LPFC neurons examined during both outcome-expectancy and spatial-memory tasks are illustrated in Fig. 9. Both reward-expectancy and omission-expectancy neurons were observed in all of the areas explored (that is, the principalis area including the lips and depths of the principal sulcus, the arcuate area and the inferior convexity area), although no clear localization was observed for either type of neuron. This was also the case for the outcome-unselective delay neurons in the outcome-expectancy task. Spatial-WM and non-directional delay neurons

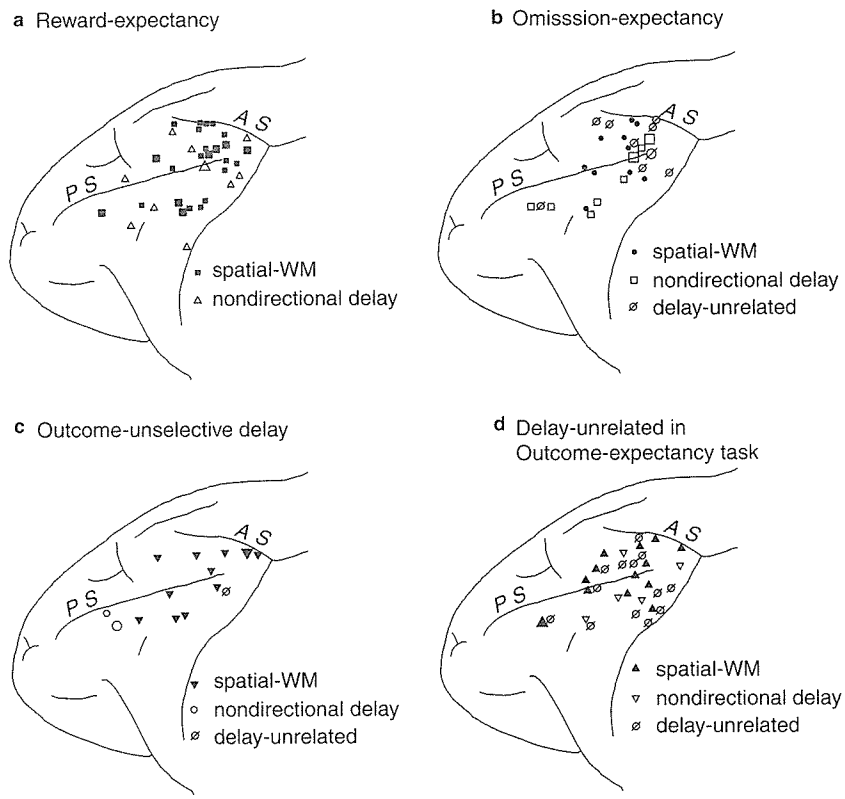

Fig. 9 Locations of penetrations of the LPFC neurons examined in both the outcome-expectancy and the spatial-memory tasks. Penetrations in the right hemisphere are plotted onto comparable locations in the left hemisphere. **a** Reward-expectancy neurons with spatial-WM (*filled squares*) and non-directional delay (*triangles*) activity during the spatial-memory task. **b** Omission-expectancy neurons with spatial-WM (*filled circles*), non-directional delay (*squares*) and delay-unrelated (*scored circles*) activity during the spatial-memory task. **c** Outcome-unselective delay neurons with spatial-WM (*filled upside-down triangles*), non-directional delay (*circle*) and delay-unrelated (*scored circles*) activity during the spatial-memory task. **d** Neurons that did not show delay-period activity during the outcome-expectancy task with spatial-WM (*filled triangles*), non-directional delay (*upside-down triangles*) and delay-unrelated (*scored circles*) activity during the spatial-memory task. *Large symbols* indicate penetrations in which two or more neurons were found

were also found in the principalis, arcuate and inferior convexity areas.

Discussion

We examined individual LPFC delay neurons in two different types of task in order to clarify the functional significance of delay-period activity during WM task performance, and particularly the functional relationship between reward/omission-expectancy and spatial-WM activity. LPFC neurons that showed delay-period activity in one task were found to be more likely to show delay-period activity in the other (83 out of 113 neurons; 73.4%). The majority of the delay neurons (104 out of 113; 92.0%) showed differential activity depending on the trial type (reward versus no-reward or left versus right); of these, 43% showed differential activity during both types of task and the remaining 57% showed differential activity during only one type of task (Table 1).

In support of our hypotheses, all of the reward-expectancy neurons showed delay-period activity during the spatial-memory task. Of these, most (35 out of 46; 76.0%) differentiated between the left and right remembered locations. However, only one-third (11 out of 31) of the omission-expectancy neurons discriminated between left and right, and one-third (11 out of 31) of the omission-expectancy neurons failed to show any significant delay-period activity, in the spatial-memory task. Viewed the other way around, neurons showing spatial selectivity during the spatial-memory task were much more likely to be reward-expectancy neurons than omission-expectancy neurons during the outcome-expectancy task.

Representation of spatial WM and reward/omission-expectancy in LPFC neurons

Spatial-WM activity and reward/omission-expectancy activity were both involved in representing not what was currently being presented, but rather what had been presented previously or would be presented later during the trial; the former was concerned with where the spatial cue was presented or which side the response should be directed to, and is thought to be involved in representing task-relevant cognitive information that guides the monkey in correct task performance in order to attain the reward, whereas the latter was concerned with what type of reward would be delivered. Even omission-expectancy neurons might have been involved in representing the reward, in the sense that although the outcome of the current trial was no-reward, the true reward was moving to a future trial. Reward-expectancy activity in prefrontal neurons has been suggested to represent ";affective WM" (Davidson 2002). However, according to the original and widely accepted definition, WM is the "temporary storage and manipulation of information for complex cognitive tasks" (Baddeley 1986). As reward-expectancy and omission-expectancy neuronal activity is neither a prerequisite nor essential for correct task performance, reward-expectancy and omission-expectancy activities are not considered to constitute neuronal substrates of WM. "Affective WM" might therefore be a misusage of the term "WM".

Recently, the effects of reward on brain activity have been examined in several areas outside of the LPFC. Reward-expectancy and omission-expectancy-related neurons have been identified in the primate orbitofrontal cortex (OFC) (Tremblay and Schultz 1999, 2000; Hikosaka and Watanabe 2000), although WM-related neurons are relatively rare in the OFC (Tremblay and Schultz 2000; Wallis and Miller 2003). Platt and Glimcher (1999) showed that the reward a monkey expects during an oculomotor task modulates the direction-selective activity of neurons in the lateral intraparietal (LIP) area. Similarly, Sugrue et al. (2004) reported that eye-movement-related neurons in the monkey LIP area represent the relative reward value of competing actions. Delay activity of monkey caudate neurons was also modulated by the presence or absence of reward during an oculomotor delayed response task, to the extent that the representation of cognitive information was sometimes overshadowed by the reward information (Kawagoe et al. 1998). The LIP and caudate nucleus are not viewed as areas in which cognitive information initially meets reward information; they might receive task-related cognitive and motivational information from the LPFC (Kawagoe et al. 1998; Platt and Glimcher 1999; Sugrue et al. 2004). Indeed, anatomical studies indicate that the LPFC receives highly processed cognitive information from the posterior-association cortices, as well as highly processed motivational information from the OFC (Barbas 1993). In a recent paper, in which neuronal activity was recorded from both the OFC and LPFC in the same monkey (Wallis and Miller 2003), reward selectivity arose more rapidly in the former than in the latter. Thus, reward information might initially enter the OFC before being passed to the LPFC, where it is integrated with cognitive information. The LPFC could therefore play important roles in modulating eye movement-related neuronal activity in the LIP and caudate nucleus areas by sending integrated cognitive and motivational information.

Reward and spatial discrimination by LPFC delay neurons

There was a weak, but statistically significant, correlation between the RNRDI and LRDI in individual LPFC delay neurons (Fig. 6). Thus, the more discriminative a certain delay neuron was between the reward and no-reward trials during the outcome-expectancy task, the better it tended to discriminate between the left and right trials during the spatial-memory task. It appears that the ability of LPFC neurons to discriminate between different events is generalized across many dimensions.

The ability of individual LPFC delay neurons to discriminate between different types of reward, as indicated by the RDDI, did not significantly differ between the outcome-expectancy and spatial-memory tasks (Fig. 7). Thus, reward discrimination appears to be consistent across WM and non-WM tasks.

Almost all spatial-WM neurons corresponded to the spatial relationship between the left, center and right keys, although the monkeys were not required to discriminate between the center and left or right keys. Thus, LPFC neurons appeared to be involved in representing the implicit spatial relationship among the three keys.

Modification of spatial-WM activity by reward-expectancy

Differential outcome effects point towards the importance of reward in controlling the discrimination task performance of an animal (Peterson 1984). Behavioral data also indicate that the RT of an animal is much shorter when a more preferred reward is used, compared with that when a less preferred reward is used (Watanabe et al. 2001). In the present study, many spatial-WM neurons showed enhanced activity when a more preferred reward was used (Fig. 8). LPFC delay neurons also showed enhanced activity when the magnitude of the reward was increased in oculomotor delayed response tasks (Leon and Shadlen 1999; Roesch and Olsen 2003). The enhancement of spatial discrimination was reported in some spatially differential delay neurons when a more preferable outcome was expected, both with respect to the presence or absence of reward (Kobayashi et al. 2002) and different magnitudes of reward (Roesch and Olson 2003).

Neurons in the caudate nucleus also showed both reward-expectancy-related and spatially differential delay activity during an oculomotor delayed response task (Kawagoe et al. 1998). Their delay-period activity, but not their spatial discrimination, was modulated depending on whether the monkey could expect the delivery of a reward.

Functional significance of the delay-period activity of LPFC neurons for WM task performance

When the bait was omitted from the cue presentation during a delayed response task, the monkeys were reluctant to respond; moreover, when they did respond, the RT became much longer. On such "dry-run" trials, sustained activity in LPFC delay neurons disappeared (Fuster 1973). The disappearance of sustained activity might reflect the absence of a representation of the reward. The characteristics of the activity changes reported in these delay neurons were similar to those of the LPFC neurons in the present experiment, which showed activations in reward, but not in no-reward, trials during the outcome-expectancy task, and showed non-directional delay activity during the spatial-memory task (Fig. 3b). Neurons with such reward/omission-expectancy and non-directional delay activity constituted 19.4% (22 out of 113) of the LPFC delay neurons examined. They do not appear to be concerned with retaining spatial information in WM, and are more likely to be concerned with motivational aspects of WM task performance. Thus, consistent with our hypothesis, a substantial number of delay neurons observed during the spatial-memory task were not directly concerned with the cognitive control of the task performance. Kobayashi et al. (2002) also reported LPFC delay neurons that did not show spatial selectivity, but showed higher or lower firing rates, under reward-present conditions compared with reward-absent conditions during an oculomotor delayed response task.

What, then, is the functional significance of non-directional delay neurons with reward/omission-expectancy activity for the WM task if their activity is not directly concerned with the cognitive control of behavior? Sustained delay activity, and particularly reward-expectancy activity with a magnitude that increases when a more preferred reward is used, might support WM task performance by raising general arousal levels and through attention control, particularly the inhibitory control of internal (perseveration) and/or external (distracting stimulus) interference.

By contrast, spatial-WM neurons without reward/omission-expectancy activity might be involved in representing only cognitive information concerning how the reward can be attained, and could be involved primarily with the cognitive control of the task performance. However, it remains uncertain whether they are concerned exclusively with retaining spatial information in WM. It was recently shown that sustained delay activity in LPFC neurons was more concerned with spatial attention than with spatial WM during a task in which a monkey was required to attend to a certain location while remembering a different location (Lebedev et al. 2004). Moreover, an imaging study reported no activation of the LPFC, but activations in the posterior visual association area, corresponding to the maintenance of object information in WM (Postle et al. 2003). Thus, it is important to note that delay-period activity in the LPFC is not necessarily associated with retaining information in WM, and that some WM tasks can be performed without sustained activity in the LPFC.

Integration of cognitive and motivational operations in the LPFC

Spatial-WM neurons with reward/omission-expectancy activity might be involved in representing both the reward itself and how it can be attained. In the present study, the enhancement of spatial-WM activity was observed in many such neurons when employing a more preferred reward. Kobayashi et al. (2002) and Roesch and Olson (2003) reported the enhancement of spatial