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研究課題２
反応抑制課題遂行時の脳活動の測定

A(2).1. 本研究の概要

行動の抑制・コントロールや、自身のパフォーマンスのモニタリングは人間の遂行機能の中で非常に重要なものである。抑制機能の低下は、状況に応じた反応の切り替えの失敗や、不適切な反応の表出として表現されやすく、日常生活にも大きな影響を与える。脳損傷例を対象とした神経心理学研究や事象関連電位(ERP)・脳機能イメージングを用いた研究から、不適切な反応の抑制には前頭前野(PFC: Prefrontal cortex)が重要な役割を担うことが示されてきた。前頭前野は、自己のモニタリング、行動のプランニング、優先度の決定といった高次な意思決定に関与すると同時に、その根底となるワーキングメモリや注意機能との強い関わりも指摘されている領域である。この領域が担う認知機能は、睡眠の質や量の低下によって最も影響を受けやすいと考えられている(Jones & Harrison, 2001; Muzur et al., 2002)。実際に、睡眠時間の減少や、睡眠に関する障害によって、言語性流暢性、創造性や計画性などを含む遂行機能の低下が観察されている（Jones & Harrison, 2001)。

このような背景から、反応抑制およびこの機能を支える脳活動に睡眠が及ぼす影響を検討することは、本研究課題の目的に照らして重要である。平成22年度は、健康な成人を対象とした反応抑制課題をMRIスキャナ内で実施し、課題の妥当性の検討、および反応制御を可能にする脳活動を支える部位を特定した。課題として、心理学、認知神経科学において反応抑制を検討するために一般的な課題であるGo/Nogo課題を採用した。この結果および先行研究から、適切な課題遂行に要求される活動が右中・下前頭領域、前頭前野内側部に見られた。また、反応抑制機能の個人差と脳活動の関連性についても検討を実施した。この結果、反応抑制の失敗率と左中前頭回、尾状核、下前頭回などの活動に負の相関関係が観察された。これらの部位は反応抑制のみでなく、記憶や学習にも関与しているおり、認知処理の効率性・流暢性を支えていると考えられる。

本年度は、これらの部位の活動および課題のパフォーマンスが、健常者における睡眠負債によってどのような影響を受けるかどうかを検討した。この試みは、睡眠障害の諸相や睡眠負債によって認知機能およびその神経基盤との関連性を詳細に明らかにすることを目指すものである。

A(2).2. 本研究の目的と背景

A(2).2.1. Go/Nogo 課題

本研究では、行動の抑制機能に関連する脳活動を特定するために Go/Nogo 課題を使用した。この課題は、反応抑制を検討するための最もシンプルなもので、複雑な認知的・行動的要素が含まれず、古典的な心理学研究・精神医学研究でも近年の機能的脳画像(fMRI)研究でも、頻繁に利用されている。Go/Nogo 課題とは、異なる二つの刺激を呈示し、被験者には一方が呈示された場合（Go 刺激）には迅速な反応を求め、もう一方が呈示された場合（Nogo 刺激）には反応をしないように求める。特に Nogo 刺激を呈示された場合の反応抑制に成功した時の神経活動が、脳内における抑制の働きを表すとして多くの研究に用いられている。

A(2).2.2. Go/Nogo 課題の遂行に伴う神経活動と関連領域

Simmonds, Pekar and Mostofsky (2008)は近年実施された Go/Nogo 課題に関する fMRI 研究のメタ解析を実施し、右中・下前頭領域(BA46/44)、右下頭頂領域(BA40)、前補足運動野を含む前頭前野内側部(BA6/32)が反応抑制に関与していることを示している。とくに、前頭前野内側部

(BA6/32)は反応の抑制だけでなく、Go 条件、Nogo 条件共に、特定の条件に応じた適切な反応の選択・表出に重要である、と提唱している。本研究班でも、昨年度に課題の妥当性検証を目的として、健常成人を対象に Go/Nogo 課題実施時の脳活動を fMRI を用いて検討を行った。この結果、適切な課題遂行に要求される活動が右中・下前頭領域、右下頭頂領域・前頭前野内側部に観察されることを明らかにしており、先行研究と非常に一貫性の高い結果を得た。

一方、Nogo 時に誤って反応をしてしまうコミッションエラーの出現時には、前部帯状回(ACC, BA24, 32)および近接した前頭前野内側部、両側の島皮質(BA13)と前頭弁蓋部(BA47)、楔前部および後部帯状回(PCC, BA7, 31, 29)の活動が増大する(Menon et al., 2001)。これらの領域は感情処理に関わる領域であることを示唆するデータが蓄積されており、特に前部帯状回の吻側部(rostral ACC)や島皮質/前頭弁蓋部は誤反応に付随した感情の生起と関連しており、より背側の前部帯状回(dorsal ACC)から前補足運動野の領域は反応葛藤の検出に関与している、と考えられている(Hester, Fassbender & Garavan, 2004)。本研究班では個人のコミッションエラー率と左中前頭回、尾状核、下前頭回などの活動に負の相関関係を観察している。これらの部位は反応抑制のみでなく、記憶や学習にも関与していることが知られている。本年度は、これらの部位の活動および課題のパフォーマンスが、健常者における睡眠負債によって影響を受けるかどうかを検討した。

A(2).2.3. Go/Nogo 課題の遂行と神経活動に及ぼす睡眠の影響

さらに、Go/Nogo 課題と ERP を用いて、睡眠と抑制機能の関係性を検討した研究では、睡眠に問題をもつ被験者群で Nogo 条件の N2 の振幅減衰、P3 の潜時増大、Go 条件での P3 の振幅減衰が観察された(Breimhorst et al., 2008)。睡眠の質による行動指標への影響はこの実験では見られなかったが、この結果は睡眠の質の低下が前運動過程の抑制処理、運動反応の抑制のスピード、課題関連情報の処理の効率性などに影響している可能性を示している。

睡眠はく奪の認知機能への影響は、個人において均一ではなく、脆弱性の高低を鑑みた検討を行う重要性が示されている(Chuah et al., 2006)。彼らは fMRI を用いて、睡眠はく奪が抑制能力に及ぼす影響について検討し、Nogo 条件の成功時の右腹外側前頭前野(BA10/46)、右島皮質前部(BA13)、失敗時の前部帯状回(BA24/32)の活動と抑制能力の間に交絡があることを示した。一方、抑制能力を問わず、睡眠はく奪は課題遂行時の注意維持時に両側腹外側前頭領域の両側の活動が低下していた。睡眠はく奪に対する脆弱性が低い群では、もともと右腹外側前頭前野の活動が低くても反応抑制に成功できるのに対して、脆弱性が高い群では同様のパフォーマンスをおさめるためには、この領域の活動量の増大が必要である。睡眠はく奪後にこの領域の活動が、脆弱性が低い群では上昇し、高い群では上昇しないために、抑制行動自体にも影響が生じると考えられる。前部帯状回は前述のように外側前頭前野と共同で活動し、反応葛藤の検出やエラーのモニタリングなど認知のコントロールに関与している。脆弱性が低い群では、Nogo 条件失敗時のこの活動が大きく、誤反応への気付きと後続する試行への注意喚起が調整されていると考えられるだろう。この研究結果は、睡眠と反応抑制の関係を検討する上で、対象となる被験者の反応抑制や注意といった認知機能をあらかじめ測定し、睡眠との関連性を検討していく必要があることを示している。

A(2).2.4. 本研究の目的

以上の結果を踏まえ、本年度は昨年度作成した課題を用いて、不眠症患者にみられる慢性的な睡眠負債の認知処理の制御、流暢性への影響

を検討するため、まず健常者を対象とした睡眠統制実験を行った。その結果について報告する。

B(2) 方法

B(2).1 被験者・断眠プロトコル

被験者、断眠プロトコルは研究課題1と同様であった。

B(2).2 刺激と課題

先行研究および昨年度に行った課題をもとにGo/Nogo 課題を作成・実施した。注視点(+)とアルファベット1文字が被験者の眼前に設置されたモニタに交互に呈示された。呈示時間は注視点が1.6秒、アルファベットが0.5秒であった。20試行を1セッションとして、セッション間の休憩12.6秒をはさみ、10 セッション実施した。被験者はアルファベットが呈示されたら、手元の反応ボタンを右手の人差指で押すように指示された。しかし、X が呈示されたときだけは反応ボタンを押さないように指示された。前者がGo条件、後者がNogo条件である。また、注視点(+)が提示されている間は被験者は反応を求められない。それぞれの試行数は、Go条件が160試行Nogo条件が40試行、総計200試行であった。(図7参照)

被験者には、可能な限り速く反応を行うように求めた。具体的にはGo条件時の平均正反応時間が300ミリ秒以内になるように努力するよう教示した。この教示は、時間的制限を設けることによって、反応制御の難易度を高くすることを意図したものである。

刺激の提示，反応記録などの実験制御はPresentation (Neurobehavioral System 社)を用いて行った。

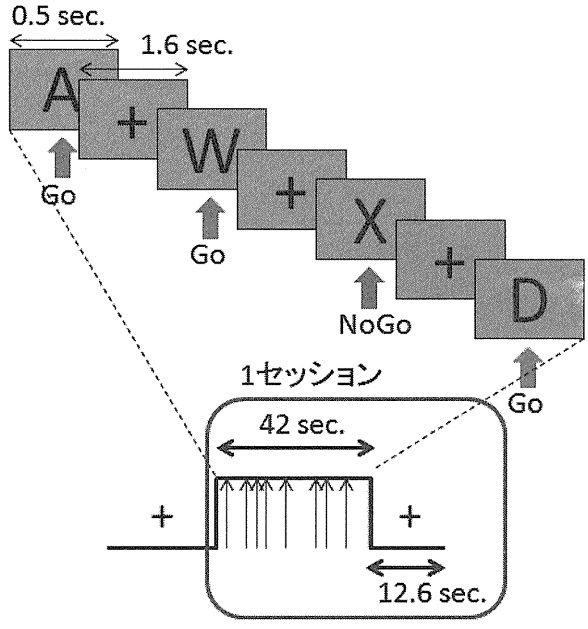

図7. Go/Nogo 課題の概要

B(1).3 データの計測と処理

本実験ではSiemens社の3T MRI Verioを用いて，被験者の脳活動を測定した。被験者のどの部分の脳活動を測定するか決定するためのスキャンを実施した後，gradient echo EPIシーケンスで機能画像を撮像した。撮像条件は以下の通りである。TR=2000ms, TE=30ms, 25 slices, FoV=192mm × 192mm (64 × 64), Slice thickness=2mm, 1 mm gap, Voxel size=3mm × 3mm × 3mm。機能画像の撮像後に，解像度1mm^{3}のT1解剖画像を被験者ごとに撮像した。機能画像はSPM8 (http://www.fil.ion.ucl.ac.uk/spm/)によって前処理(slice timing correction, realignment, coregistration, segmentation, normalize, smoothing)をおこなった。機能画像撮像時の被験者の体動によるアーチファクトの除去、補正も実施した。その後、個人レベルおよび集団レベルの解析を行った。

個人レベルの解析では、各被験者において、Go条件、Nogo条件の成功時に対応する脳活動を特定した。各反応に応じた脳活動の特定のた

めに、血流反応動態関数(hemodynamic response function:HRF)を利用した。その後、個人レベルの解析結果をもとに、集団レベルの解析を実施した。

睡眠負債の影響を調べるために、睡眠充足条件(Control条件)、睡眠負債条件(SD)で同様の課題を行い、行動データおよび脳活動データの比較を行った。

C(2). 結果

C(2).1 行動データ

Control条件における参加者14名のGo条件平均成功試行数は156.6試行、平均反応時間は313.61ms(±38.75ms)であった。一方Nogo条件における平均成功試行数は26.2試行、コミッションエラー試行数は13.8試行であった。すなわち、平均コミッションエラー率は0.35であった。また、コミッションエラー時の平均反応時間は288.32ms(±44.34ms)msであった。

SD条件時のGo条件-平均成功試行数は158.9試行、平均反応時間は330.07ms(±29.01ms)であった。一方Nogo条件における平均成功試行数は27.7試行、コミッションエラー試行数は12.3試行であった。すなわち、平均コミッションエラー率は0.30であった。また、コミッションエラー時の平均反応時間は302.12ms(±27.18ms)msであった。

睡眠負債がGo/Nogo課題の実行に及ぼす影響を検討するために、睡眠条件(Control・SD)を要因とする、コミッションエラー反応率に対する1要因分散分析を実施した。この結果、Control群とSD条件の間に有意な違いは見られなかった($F(1,13)=.88$ $p=.36$ *n.s.*)。(図8参照)

一方、平均反応時間に対して、睡眠条件(Control・SD)と試行条件(GoNogo)を要因とした2要因分散分析を実施したところ、睡眠条件($F(1,13)=5.13$ $p<.05$)、試行条件($F=31.61$ $p<.0001$)ともに主効果が認められた。下位検定の結果、SD条件における反応時間はControl条件よりも長く、またGo条件の反応時間はNogo条件の反応時間(コミッションエラー時)よりも長かった。(図9参照)

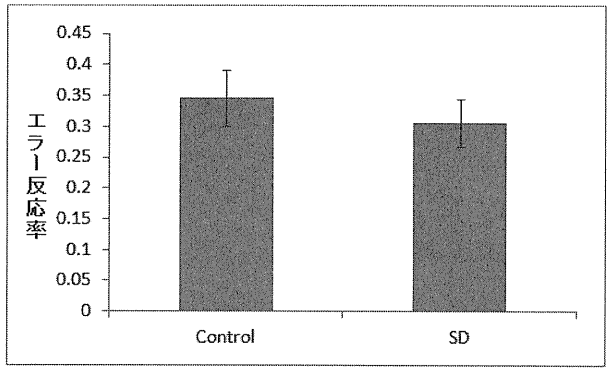

図8 睡眠条件ごとのコミッションエラー率
注:図中のバーは標準誤差を示す

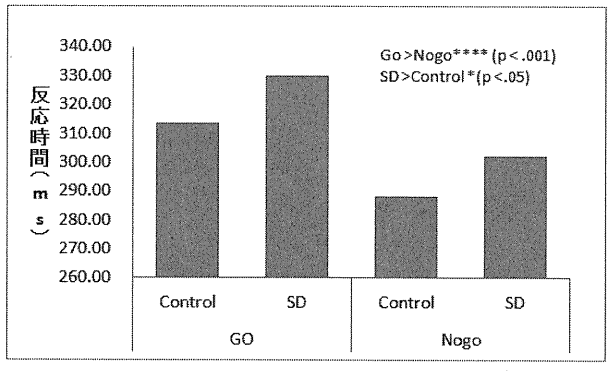

図9 睡眠条件・試行条件ごとの平均反応時間

C(2).2 脳機能画像データ

—反応抑制に関与する部位—
(Go条件Nogo条件成功時の脳活動)

反応抑制に関与する脳活動として、Control・SD条件に共通してGo条件、Nogo条件の成功試行に対応する脳活動を特定した。Go条件では、左運動野周辺領域、右小脳といったボタン反応の表出に関わる脳部位と同時に、帯状回前部、右中前頭回など運動制御に関わる脳部位の活

動が特定された。

一方、Nogo 条件の成功時には、両側前頭弁蓋部/前部島皮質、両側補足運動野、前部帯状皮質の活動が観察された。先行研究では、これらの部位が文脈に応じた反応の選択と遂行のために重要な役割を担っていることが示されており、本研究の結果も一致性の高いものであったと言えるだろう。

Go 条件 Nogo 条件ともに活動が特定された脳活動は、昨年度の研究でも特定されたものであり、課題の妥当性・頑健性は確認された。

—睡眠条件による Go 条件時の脳活動の違い—

睡眠負債が反応制御に及ぼす影響を検討するために、Go 条件・Nogo 条件時における睡眠条件の違いを確認した。

まず、Go 条件時における Control 条件時と SD 条件時の違いを検討したところ、Control 時の方が大きな活動が見られた領域はなかった。一方、SD 条件では、Control 条件よりも右上部/下部頭頂葉、右下頭頂葉領域の活動が増大していた（p<.001, k>10, *uncorrected*）。（表 1： 参照）

—睡眠条件による Nogo 条件時の脳活動の違い—

つぎに Nogo 条件時における Control 条件時と SD 条件時の違いを検討した。図 10 に示す通り、Control 時よりも SD 時に両側前頭弁蓋部/前部島皮質、両側補足運動野、前部帯状皮質が広範囲にわたる強い活動がみられた。これらの領域はすべて、Nogo 条件時に反応を適切に抑制することに関与が認められた領域である。

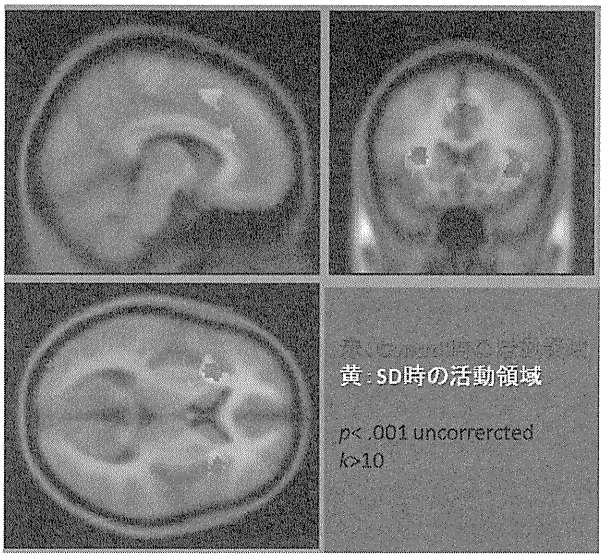

図 10 Nogo 条件時の Control 条件と SD 条件の活動領域の比較（x=8, y=17, z=6）

D(2)． 考察

本年度は、不眠症患者にみられる慢性的な睡眠負債が認知処理の制御や流暢性に及ぼす影響を検討するために、彼らのモデルとなる睡眠統制条件下の健常者を対象に、Go/Nogo 課題を実施した。

本研究において、睡眠負債時（SD 条件）では、充足時（Control 条件）に比べて、課題で要求された反応までに要する時間が延長するが、エラー反応率は増加しなかった。加えて、この際の脳機能画像に注目すると、SD 条件では、Control 条件よりも、Go 試行・Nogo 試行ともに正反応の表出に関わる脳活動が大きいことが明らかになった（表 1・図 10）。

本研究で得られた結果を総合すると、睡眠負債時に、睡眠充足時と同様のパフォーマンスをおさめるためには、注意・反応制御といった処理

表 1：GO 条件時に SD 条件で Control 条件よりも活動が増大した部位

Region of activation	L/R	BA	Number of voxels in cluster	z	MNI		
					x	*y*	*z*
Superior/inferior parietal lobule	R	7/40	110	3.91	50	-60	52
Inferior frontal gyrus	R	47	20	3.42	46	46	-6
Putamen	R	-	22	3.39	22	18	-8
Pallidum	L	2	11	3.37	-16	2	-2

(p < .001, k>10, uncorrected)

に必要となる認知的資源がより多く求められ、当該処理に関わる脳領域の活動増大がこの過程を支えている、と理解できる。

Nogo 条件（反応の抑制を要する時）で観察された睡眠負債時の右外側下前頭前野、帯状回前部/内側前頭皮質、両側島皮質の活動増大きいに注目すると以下のような考察が可能であろう。右外側下前頭前野は、能動的な注意の切り替えへの関与が認められている。同様の課題を実施した先行研究(Chuah et al., 2006)では、Nogo 反応の成功とその活動量に関連が認められる部位である。昨年度に本研究班が実施した実験では、この部位の個人の活動量と Nogo 試行成功率に正の相関が認められた。すなわち、この部位は課題遂行に必要となる注意のコントロールを担い、反応するべき Go 刺激への反応表出、および、反応を必要としない Nogo 刺激に対する反応を抑制することに必要であると考えられる（Chuah et al., 2006）。

前部帯状回/内側前頭皮質は、自身の反応のモニタリング（それぞれの刺激に対してするべき反応ができているか）を支え、反応時の葛藤の検出や、表出する反応を調整する役割も担っていると指摘されている。本研究で使用した課題では、ほとんどの試行が Go 試行なので、反応の実施がデフォルトになり、Nogo 試行ではこのデフォルト反応を抑制することが求められる。このため、反応をしたいけれども抑えなければいけない、という葛藤が生じる。この葛藤を検出し、反応抑制を実現するといった一連の過程が、睡眠負債時にはより負荷の高いものになっている、ということができるだろう。

島皮質については様々な議論が考えられるが、前部帯状回と同時に活動し、身体の緊張状態を高めることによって、検出された葛藤にもとづき、反応の抑制を可能にしている、と理解することが出来る。ある程度の緊張状態は認知処理に促進的な効果を及ぼすことが指摘されており、このような背景的な役割を果たしているとも考えられる。

ここでもう一度、行動データに立ちかえると、脳機能画像データには睡眠負債時・充足時で顕著な差があるにもかかわらず、エラー反応率の上昇は認められない。その代わりに、反応時間の遅延が生じている。脳活動の増大および反応時間の遅延は、睡眠負債によって低下した認知的処理の流暢性に対する補償作用であることが示唆される。

本実験の参加者は、比較的若く（平均 24 歳）実際に不眠症を罹患する患者群の年齢よりも若いことに注意するべきであろう。若年者は高齢者に比べて、自身の認知処理の特性を俯瞰的に捉えるメタ認知能力・モニタリング能力に優れており、睡眠負債によって生じた認知処理の流暢性の低下を鋭敏に察知していたと仮定できる。しかし、恒常的にメタ認知能力の低下が見られる高齢者や、精神疾患の罹患者では、自身の処理の流暢性低下への気付きも悪いことが予測できる。このような特性を持つ個人が不眠症状に陥った場合は、メタ認知による補償作用が機能せず、認知処理の不具合がそのまま行動として表出される可能性が考えられる。注意の制御をより強く求められる場面においては、この傾向がさらに顕著に見られるであろう。具体的な事象として、運転、料理や仕事といった複数の処理の同時遂行が求められる場面における誤操作や誤反応が想定できる。このような機能低下は、結果として彼らの日常生活の質（QOL）を著しく低下させることに直結するだろう。今後このような若年以外の対象者に同様の実験を行った上で、その機能不全を描出できるかも知れない。

上記を踏まえ、今後検討するべき課題としては以下のようなものがあげられる。①より高齢の健常者を対象とした睡眠負債条件下における課題の実施、検討、②メタ認知能力の高低が、睡眠負債時のパフォーマンス維持あるいはエラーの増加に及ぼす影響の検討、③実際に不眠症を罹患している患者を対象とした課題の実施、検討、④睡眠負債への脆弱性を規定する要

因の解明、⑤より難易度が高く(並行課題など)日常生活場面を模した課題を用いた検討。このうち、③については今年度、予備的な調査の実施に着手しているが、来年度はより重点を置く必要がある。また、②および④、⑤についても、不眠症、あるいは睡眠負債への脆弱性が高い個人における QOL 上昇の糸口を見出すために、次年度以降、推進の必要性が高いと考えている。

E(2). 結語

本研究では、反応抑制およびこの機能を支える脳活動に睡眠が及ぼす影響を明らかにするために、課題のパフォーマンスが、健常者における睡眠負債によってどのような影響を受けるかを検討した。この結果、睡眠負債時に、睡眠充足時と同様のパフォーマンスをおさめるためには、注意・反応制御といった処理に必要となる認知的資源がより多く求められ、当該処理に関わる脳領域の活動増大がこの過程を支えている、と考えられた。本実験の参加者は、比較的若く、メタ認知能力の低下が想定されないために、このような補償作用が観察されたと考えられる。しかし、実際に不眠症を罹患する患者群の年齢がより高齢であること、また日常生活ではより複雑な認知処理が想定されることから補償作用が機能しない事態が想定される。

上記を踏まえ、今後以下の課題についての研究、検討の実施を推進していく必要がある。①より高齢の健常者を対象とした睡眠負債条件下における課題の実施、検討、②メタ認知能力の高低が、睡眠負債時のパフォーマンス維持あるいはエラーの増加に及ぼす影響の検討、③実際に不眠症を罹患している患者を対象とした課題の実施、検討、④睡眠負債への脆弱性を規定する要因の解明、⑤より難易度が高く(並行課題など)日常生活場面を模した課題を用いた検討。これらの研究成果は睡眠負債によって生じ得る反応抑制への影響を精緻に理解し、症例への助言や治療プログラムの開発のために有用なものになるであろう。

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H. 知的財産権の出願・登録状況

なし

F. 健康危険情報

特になし

G. 研究発表

G-1. 論文発表

なし

G-2. 学会発表

元村祐貴、大場健太郎、寺澤悠理、片寄泰子、北村真吾、榎本みのり、守口善也、樋口重和、三島和夫：部分断眠による睡眠負債が情動反応に与える影響:機能的MRIを用いた検討, 日本生理人類学会第65回大会, 大阪, 2011年11月

Ⅲ．研究成果の刊行に関する一覧表

雑誌

発表者氏名	論文タイトル名	発表誌名	巻号	ページ	出版年
Komada Y, Abe T, Okajima I, Asaoka S, Matsuura N, Usui A, Shirakawa S, Inoue Y.	Short Sleep Duration and Irregular Bedtime Are Associated with Increased Behavioral Problems among Japanese Preschool-Age Children.	Tohoku J Exp Med	224(2)	127-136	2011
Okajima I, Komada Y, Nomura T, Nakashima K	Insomnia as a risk for depression: A longitudinal epidemiological study on a Japanese rural cohort	J Clin Psychiatry	73(3)	377-383	2011
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Ⅳ. 研究成果の刊行物・別刷

Tohoku J. Exp. Med., 2011, **224**, 127-136

Short Sleep Duration and Irregular Bedtime Are Associated with Increased Behavioral Problems among Japanese Preschool-Age Children

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Sleep problems are known to be risk factors for subsequent emotional and behavioral difficulties in childhood and adolescence. To date, there has been no study investigating the relationships between sleep habits and behavioral problems in a large nonclinical sample of preschool age children. The aim of this study was to examine these relationships and factors associated with the sleep habits of preschool age (2 to 5 year old) children. Their mothers (n = 1,746) completed a multiple-choice questionnaire about the sleep habits and behavior problems of their children, as well as their own sleep habits and working hours at Tokyo metropolitan public nursery schools. The short sleep duration group showed significantly higher aggressive scores than the long sleep duration group among 2- to 3-year-old children, and the irregular bedtime group showed significantly higher aggressive and attention problem scores than the regular bedtime group among 4- to 5-year-old children. Univariate and multivariate logistic regression analyses revealed that children's late bedtime was associated with their mother's late waking-up time, and late schedule of both the mother's leaving and returning home. This study recognized an association between behavioral problems and poor sleep habits among preschool-age children. It is important for children to sleep regularly and adequately in order to decrease their behavior problems. In conclusion, appropriate management of children's sleep by their mothers is necessary for promoting sleep-related health of children.

Keywords: behavior problems; child; child behavior checklist; parents; sleep habits
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Nocturnal sleep onset has become later and sleep duration has been progressively shortened in the last few decades (Aldrich 2003). Chronic insufficient sleep and sleep loss are common problems in modern industrial societies because annual work hours have become extended and a larger number of people are engaged in shift-work compared with the past (Aldrich 2003). Consistent with these trends in adults, bedtime has become progressively delayed, and sleep duration shortened among adolescents and children in industrial countries (Kohyama et al. 2002; Gangwisch et al. 2010; Asaoka et al. 2010). Studies conducted in a suburban area of Tokyo showed that the proportion of 3-year-old children going to bed at 10 PM or later increased from 22% in 1980 to 50% in 2000 (Okawa and Uchiyama 1998; Kohyama et al. 2002).

Sleep plays an important role in children's development (Gregory and O'Connor 2002; Roberts et al. 2002). Sleep problems are risk factors for subsequent emotional and behavioral difficulties in childhood and adolescence (Gregory and O'Connor 2002; Roberts et al. 2002; Gregory et al. 2008). Short sleep duration and sleep disturbance are associated with higher scores of emotional lability in school-age children (Rosen et al. 2004; Nixon et al. 2008). Several other groups have shown reduced attention, impaired school performance, and hyperactivity in school-age children caused by sleep disorders (Owens et al. 1998; Gottlieb et al. 2004). These findings demonstrate the association between sleep disorders and behavioral difficulties (Breslau et al. 1996; Gregory and O'Connor 2002; Roberts et al. 2002).

Several studies have also been performed on younger children. The association between sleep problems, espe-

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cially night waking and settling problems, and behavior problems was found in preschool age children (Richman et al. 1982). A correlation between toddlers' sleep (n = 31; mean age: 18.5 months, range: 11 to 27 months) and temperament reported by mothers, especially between shorter sleep duration and less adaptability, has also been found (Scher et al. 1992). Atkinson et al. (1995) reported that toddlers with sleep problems such as night awakening had more difficulty with temperament. Bates et al. (2002) measured 4- to 5-year-old children's sleep patterns and their adjustment to the preschool environment among a predominantly low-income, community sample (n = 200), and found that disrupted sleep patterns predicted less optimal adjustment. In short, sleep problems are associated with not only adjustment problems in school-age children but also dysfunction of temperament and adjustment in preschool-age children. However, the samples in the papers referenced above were small in number. So far, there has been no study investigating the relationship between sleep habits and behavioral problems that have a profound impact on school adjustment (de Paul and Arruabarrena 1995; Davies et al. 2008) in a large nonclinical sample of preschool-age children. It could be hypothesized that behavioral problems such as lack of attention, aggressive behavior, and depression/anxiety are linked to deterioration of sleep habits. This study set out to clarify this hypothesis, focusing on preschool-age children.

Sleep habits and sleep behavior in children are influenced by many factors; e.g., biological, psychological, cultural, social, and family factors (Stores 1999; Liu et al. 2003; Komada et al. 2009). A recent study suggested that parents have a significant influence on the time of sleep onset and sleep maintenance for young children, with significant differences in parenting behaviors across cultural groups (Mindell et al. 2010). Among children who are predominantly Caucasian, the most common behavior occurring at bedtime is falling asleep independently in their own bed (57%), but the rate is clearly lower (4%) in children living in predominantly Asian regions (Mindell et al. 2010). Our previous study showed that parents of 1- to 5-year-old children with evening irregular sleep had significantly more irregular sleep habits than parents of children with morning regular sleep (Komada et al. 2009).

These findings suggest that the sleep habits of children, especially in Asian regions, are strongly influenced by those of their parents. Considering this, another aim of our study was to elucidate whether sleep habits and working hours of parents influence the sleep habits of children, such as sleep duration and bedtime of preschool-age children.

Methods

Subjects and procedure

A questionnaire survey was conducted from June to August 2007 among 40 randomly selected public nursery schools in Minato, Shibuya, and Koto Wards all of which are located in Tokyo. Public nursery schools in Japan are intended for children of parents who are engaged in regular work. Except for Sundays and holidays, the nursery schools open from early morning (7:24 ± 0:08, mean ± S.D.) till evening (18:25 ± 0:07), and offer overtime childcare till night (19:44 ± 0:30). Nursery hours are individually determined based on the commuting time and working schedule of parents. The nursery schools routinely set a nap schedule for children in the afternoon, based on the advice of the Ministry of Health, Labor, and Welfare. The average nap duration in nursery schools is 2 hours for 2- to 3-year-old children and 1.5 hours for 4- to 5-year-old children. The subjects targeted in this study were mothers of children who belonged to 2- to 5-year-old children classes; 0- to 1-year-old children classes were not targeted in this study, because the Child Behavior Check List (Achenbach 1991, 1992) we used in this study, as described later, is indicated for children aged 2 years or over. In this study, all participants were mothers, since the main childcare provider in the family is predominantly the mother in Japan (Fujimi and Nishino 2009). After thorough explanation of the purposes of this survey, mothers of 1746 children (43.1% girls) gave their written informed consent to take part in this investigation. Data on age, income, and educational background of parents were not obtained because of privacy-protection considerations. The nursery staff then gave the questionnaires to mothers, and retrieved them within 10 days. The study was approved by the ethics committee of the Neuropsychiatric Research Institute.

Measures

The main components of questionnaire items were as follows: (1) Sleep habits of children; (2) Child Behavior Check List; (3) Pittsburgh Sleep Quality Index (PSQI) (Buysse et al. 1989; Doi et al. 2000); (4) Parental Bonding Instrument (PBI) (Parker 1979); (5) Information regarding parents' daily life schedule. Mothers answered numerically or completed the multiple-choice questions about the following categories.

(1) Sleep habits of children over a recent typical month: Children's bedtime, waking-up time, sleep duration, bedtime regularity, sleep latency, number of episodes of waking up after bedtime on both weekdays and weekends were answered numerically. Questions about bedtime regularity had four possible categories (i.e., regular, moderately regular, moderately irregular, and irregular).

(2) Child Behavior Check List (CBCL): We used an international standardized method, a CBCL validated Japanese version for 2- to 3-year old children (Achenbach 1992; Nakata et al. 1999) and for 4- to 18-year-old children (Achenbach 1991; Itani et al. 2001), to evaluate attention problems, aggressive behavior, and the anxious/depressed category in children (Achenbach 1991, 1992). Subjects answered each question by selecting one of three choices of answers (i.e., not true, somewhat or sometimes true, and very true or often true). It has been previously identified that the higher the score, the greater the likelihood of problematic behavior in that scale (Achenbach 1991, 1992).

(3) Pittsburgh Sleep Quality Index (PSQI): We used the validated Japanese version of the PSQI in order to evaluate the mothers' sleep disturbance/problems i.e. difficulties falling asleep, initiating sleep, and maintaining sleep (Buysse et al. 1989; Doi et al. 2000). The Japanese version of the PSQI was developed by Doi et al. (2000), and a mean score for each component in both their control group and primary insomnia was indicated in their report (Doi et al. 2000). The PSQI included sub-items evaluating sleep quality (C1), sleep latency (C2), sleep duration (C3), habitual sleep efficiency (C4), sleep disturbance (C5), use of sleeping medication (C6), and daytime dysfunction

(C7). The cut-off score of PSQI for insomnia was already determined to be 5.5 points (Doi et al. 2000). Therefore, in this study, responders with PSQI scores of 6 or higher were considered as poor sleeper.

(4) Parental Bonding Instrument (PBI): PBI assesses parental attitude toward child rearing (Parker 1979). It consists of 25 questions categorized into 2 scales: (a) care and (b) overprotection. Care (tapping into affection and warmth) is measured with 12 items such as "I speak to my child in a warm and friendly voice," and overprotection is measured with 13 items such as "I try to control everything my child does." Subjects answered each question by selecting 1 of 4 choices (i.e., very true, moderately true, moderately untrue, and very untrue).

(5) Information regarding daily life schedule: We asked about the parents' usual time of both leaving and returning home.

Data analyses

At first, we plotted the data of the relationship between bedtime on weekdays and the T score of behavioral problems. Pearson's simple correlation coefficient was used to assess the relationships. In addition, we investigated the relationship between children's sleep habits and behavioral problems. For the analysis, bedtime was divided into the early and late groups by the median value (2- to 3-year-old children: 21:40; 4- to 5-year-old children: 22:00). Sleep duration was also divided into short and long groups by the median value (2- to 3-year-old children: 9.5 h; 4- to 5-year-old children: 9.3 h). Bedtime regularity was divided into regular and irregular groups based on the mothers' answers. Children with regular or moderately regular bedtime were classified as regular and the other was irregular. Scores of three subscale items of the CBCL; attention problems, aggressive behavior, and the anxious/depressed category; were compared between the 2 respective groups of the above sleep habits categories. Comparisons between two groups were performed by Student's *t* test.

Secondly, factors associated with the sleep habits of children were examined by a series of logistic regression analyses. All variables were initially examined in univariate models. To control for confounding factors and to determine the main correlates, we then performed multivariate logistic regression analyses for all variables that showed a significant correlation in univariate models. Statistical tests of the regression estimated odds ratios (ORs) were based on Wald statistics. Odds ratios and their 95% confidence intervals (CIs) were presented to show the association.

All statistical analyses were conducted on SPSS version 11.5.1J software for Windows (SPSS Inc., Chicago, IL, USA), and a p value of less than 0.01 was considered to indicate a statistically significant difference.

Results

A total of 2,682 eligible children whose mothers were requested to participate, mothers of 1,746 children (2- to 3-year-old classes: n = 905; 4- to 5-year-old classes: n = 841) consented to take part in this study and completed the questionnaires (response rate = 65.1%). The collection rate in 2- to 3-year-old children classes was significantly higher than that in 4- to 5-year-old children classes (68.5% vs 61.8 %, $\chi^2(1) = 13.5$, $p < 0.01$). More mothers of boys agreed to participate than those of girls (mothers of boys, 56.9%; mothers of girls, 43.1%). Average T score ± standard deviation (S.D.) of the 3 scales of the CBCL, i.e., attention problems, aggressive behavior, and the anxious/depressed category, were 55.0 ± 8.0, 56.4 ± 7.9, and 56.5 ± 7.2, respectively. The average PSQI score ± S.D. of the mothers was 4.8 ± 2.7. Mean scores ± S.D. for care and overprotection on the PBI were 41.3 ± 4.3 and 24.0 ± 4.5, respectively.

Sleep habits

Table 1 shows the sleep habits of children in both 2- to 3-year-old classes and 4- to 5-year-old classes on weekdays and on weekends, respectively. Average bedtime on weekdays was 21:41 in 2- to 3-year-old classes, and 21:51 in 4- to 5-year-old classes. On weekends, children went to bed about 10 min later, and woke up about 30 min later than on weekdays. The difference in sleep length between weekdays and weekends was 18 minutes in 2- to 3-year-old classes and 16 minutes in 4- to 5-year-old classes. The number of children whose bedtime regularity was "irregular" or "moderately irregular" was 170 of 900 (18.9%) in 2- to 3-year-old classes, and 175 of 832 (21.0%) in 4- to 5-year-old classes.

Average sleep onset time, wakeup-time, and nocturnal sleep length of mothers were 23:20 ± 1:17, 6:26 ± 0:50, and 6:43 ± 1:09, respectively. Average time of leaving home and returning home were 8:36 ± 0:55 and 18:15 ± 1:21 for mothers, and 8:22 ± 1:48 and 21:33 ± 2:32 for fathers, respectively.

Effects of sleep habits on behavior problems

Relationship of the T score of attention problem and

Table 1. Sleep habits of children in both 2- to 3-year-old classes and 4- to 5-year-old classes.

	2- to 3-year-old class			4- to 5-year-old class		
	Mean	SD	Range	Mean	SD	Range
Sleep onset time (weekdays)	21:41	0:41	19:00 - 25:00	21:51	0:44	19:00 - 24:00
Sleep onset time (weekends)	21:55	0:46	19:00 - 25:00	22:06	0:48	18:30 - 24:30
Wake-up time (weekdays)	7:06	0:35	5:20 - 9:00	7:11	0:34	5:50 - 9:50
Wake-up time (weekends)	7:38	0:51	5:30 - 13:00	7:42	0:50	6:00 - 11:30
Nocturnal sleep length (weekdays)	9:25	0:38	7:10 - 12:00	9:19	0:39	7:20 - 12:00
Nocturnal sleep length (weekends)	9:43	0:46	6:00 - 13:00	9:35	0:45	7:00 - 12:30
Difference in sleep length between Weekday and weekend	0:18	0:42	−3:00 - 4:00	0:16	0:46	−3:00 - 4:00

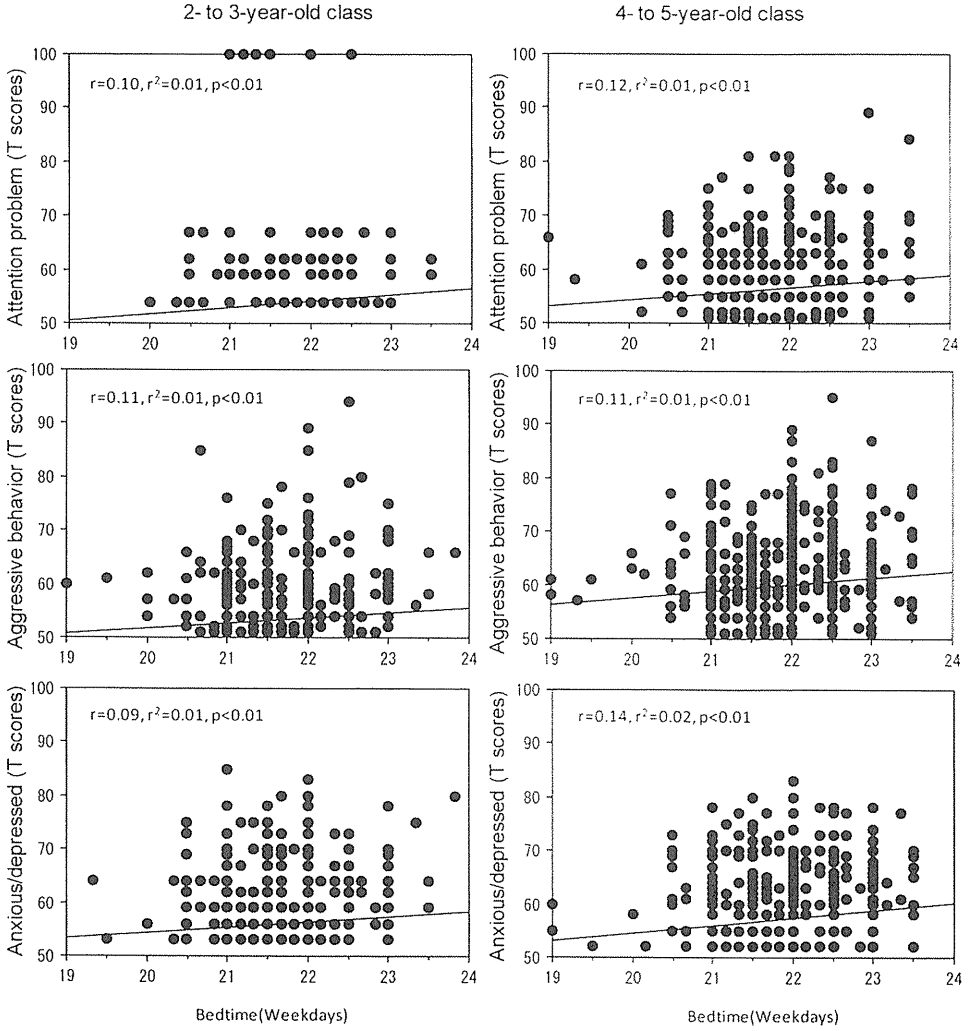

Fig. 1. Correlation between bedtime on weekdays and T score of the attention problem, aggressive behavior, and anxious/depressed.

bedtime on weekdays are illustrated in Fig. 1. The standardized regression coefficients between bedtime and attention problem among 2- to 3-year-old children and 4- to 5-year-old children were 0.10 ($p < 0.01$) and 0.12 ($p < 0.01$), respectively.

We investigated the relationship between children's sleep habits and their behavioral problems (Fig. 2). T scores of three subscale items of the CBCL versions for 2- to 3-year-old children and for subjects 4-18 years old; attention problems, aggressive behavior, and the anxious/depressed category; were compared between the 2 groups (early and late bedtime groups: Fig. 2-(a) and (b); long and short sleep duration groups: Fig. 2-(c) and (d); regular and irregular bedtime groups: Fig. 2-(e) and (f)). As for sleep duration, the shorter group showed significantly higher scores of aggressive behavior problems than the longer group in 2- to 3-year-old children [$t(873) = 2.73$, $p < 0.01$, Fig. 2-(c)]. As for bedtime regularity, the irregular group showed significantly higher attention problem and aggressive problem scores in 4- to 5-year-old children (attention problem: $t(745) = 2.74$, $p < 0.01$; aggressive problem: $t(719) = 2.67$, $p < 0.01$, Fig. 2-(f)).

Associated factors for sleep habits of children

We investigated the associated factors for sleep habits of preschool -age children (2- to 5-year-old children) including late bedtime on weekdays, short sleep duration on weekdays, and irregular bedtime. Univariate logistic regression analyses were performed on 9 independent variables: sleep habits of the mother, the PSQI and the PBI score of the mother, daily life schedule of respective parents. Among these variables, 4 items (i.e., bedtime, wakeup-time, time of both leaving and returning home of the mother) were significantly associated with late bedtime of children. To control for confounding factors and to determine the main correlates of late bedtime, the above 4 significant variables in the univariate models were subjected to multivariate analysis. Adjusted ORs and the 95% CIs in the final model are shown in Table 2. Multivariate logistic regression analysis revealed that bedtime delay of

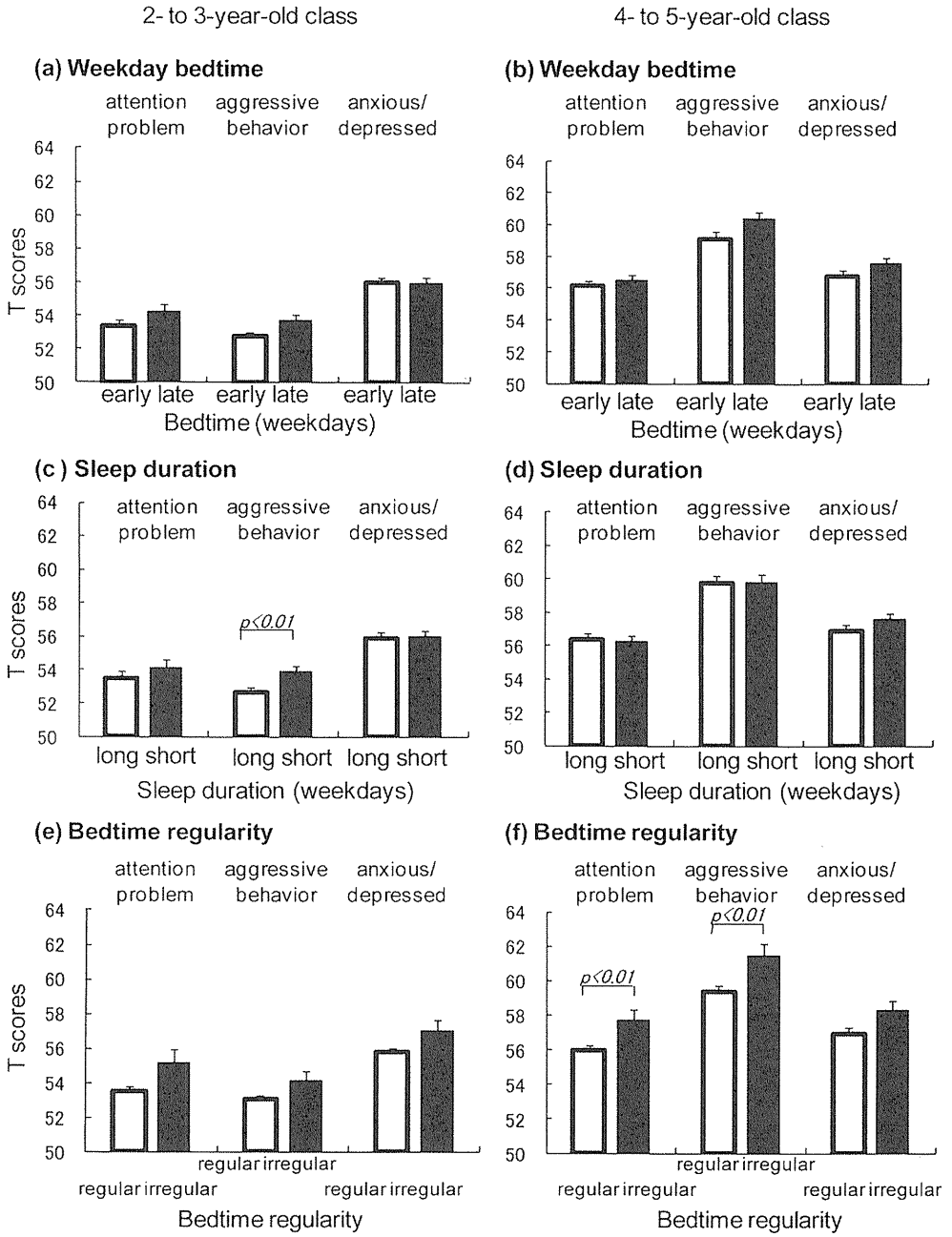

Fig. 2. Relationship between children's sleep habits and behavioral problems. Shown are the relationship between children's sleep habits and behavioral problems in 2- to 3-year-old children (left panels; a, c, and e) and 4-to 5-year-old children (right panels; b, d, and f.)

children was significantly associated with mothers' wakeup-time (OR = 1.67, 95% CI: 1.29-2.17) as well as mothers' time of leaving and returning home (OR = 1.58, 95% CI: 1.21-2.07, OR = 2.56, 95% CI: 2.00-3.28, respectively). As for PSQI sub-items, there were no significantly associated factors identified by multivariate logistic regression analysis, although the univariate models revealed that bedtime delay of children was significantly associated with mother's sleep quality (OR = 1.29, 95% CI: 1.12-1.48), sleep latency (OR = 1.21, 95% CI: 1.08-1.35), and daytime dysfunction (OR = 1.21, 95% CI: 1.07-1.36).

Five items (i.e., wake-up time, time of leaving and returning home of mother, and those of the father) among all the 9 variables were shown to be significantly associated with short sleep duration of children by univariate logistic regression analyses. Adjusted ORs and the 95% CIs in the final model are shown in Table 3. Multivariate logistic regression analysis revealed that short sleep duration of children was significantly associated with wake-up time of mother (OR = 0.71, 95% CI: 0.55-0.91), and time of both leaving and returning home of the mother (OR = 0.61, 95% CI: 0.47-0.79, OR = 1.84, 95% CI: 1.45-2.34, respectively).

Table 2. Results of univariate and multivariate logistic regression analyses of associated factors for children's late bedtime on weekdays.

	Total	Stay up late*1		Univariate Relative Risk (95% CI) *2	p	Multivariate Relative Risk (95% CI) *2	p
	n	n	%				
Maternal factors							
Bedtime *1							
Early	729	336	46.1				
Late	967	544	56.3	1.50 (1.24-1.83)	< 0.0001		ns
Wakeup-time *1							
Early	745	321	43.1				
Late	955	558	58.4	1.86 (1.53-2.26)	< 0.0001	1.67 (1.29-2.17)	< 0.001
PSQI *3							
< 6	1,149	575	50.0				
>= 6	516	290	56.2		ns		ns
Care score of PBI *1,4							
>= 42	915	464	50.7				
< 42	734	392	53.4		ns		ns
Overprotection score of PBI *1,4							
< 24	765	382	49.9				
>= 24	889	477	53.7		ns		ns
Time of leaving home *1							
Early	701	318	45.4				
Late	913	513	56.2	1.54 (1.26-1.88)	< 0.0001	1.58 (1.21-2.07)	< 0.001
Time of returning home *1							
Early	783	334	42.7				
Late	848	507	59.8	2.00 (1.65-2.44)	< 0.0001	2.56 (2.00-3.28)	< 0.0001
Paternal factors							
Time of leaving home *1							
Early	551	259	47.0				
Late	933	490	52.5		ns		ns
Time of returning home *1							
Early	627	327	52.2				
Late	788	394	50.0		ns		ns

*1 Categories were divided according to the median. *2 Relative risks approximated to odds ratio. CI denotes confidence intervals.
*3 Pittsburgh sleep quality index. *4 Parental bonding instrument.

As for mothers' PSQI sub-items, no items appeared as statistically significant factors for children's short sleep duration by both the univariate and multivariate logistic regression analyses.

With respect to irregular bedtime, 4 items (i.e., bedtime, wake-up time, the PSQI score, time of leaving home of the mother) among all the 9 variables exhibited significant association in univariate logistic regression analyses. Multivariate logistic regression analysis revealed that bedtime regularity of children was significantly associated with the mother's bedtime (OR = 1.58, 95% CI: 1.14-2.20), and time of leaving home (OR = 1.59, 95% CI: 1.13-2.23, Table 4). Among the PSQI sub-items, there were no significantly associated factors identified by multivariate logistic regression analysis, although the univariate models revealed that irregular bedtime of children was significantly associated with mother's sleep quality (OR = 1.51, 95% CI: 1.27-1.80), sleep latency (OR = 1.25, 95% CI: 1.10-1.42), use of sleeping medication (OR = 1.37, 95% CI: 1.14-1.64), and daytime dysfunction (OR = 1.34, 95% CI: 1.16-1.54).

Discussion

We investigated the associations between children's sleep habits and behavioral problems using the CBCL questionnaire, which is an international standardized method to evaluate children's behavior problems. Several studies using the CBCL questionnaire have shown that children with sleep-disordered breathing showed behavioral problems including anxious/depressed mood (Aronen et al. 2009), aggressive behavior, and social problems (Lim et al. 2008). A preliminary study also using this questionnaire in Japan has revealed that late and irregular sleepers were

Table 3. Results of univariate and multivariate logistic regression analyses of associated factors for children's short sleep duration on weekdays.

	Total	Short sleep duration*1		Univariate Relative Risk (95% CI) *2	p	Multivariate Relative Risk (95% CI) *2	p
	n	n	%				
Maternal factors							
Bedtime *1							
Early	729	359	49.2				
Late	967	449	46.4		*ns*		*ns*
Wakeup-time *1							
Early	745	422	56.6				
Late	955	387	40.5	0.52 (0.43-0.63)	*< 0.0001*	0.71 (0.55-0.91)	*< 0.01*
PSQI *3							
<6	1,149	561	48.8				
>=6	516	236	45.7		*ns*		*ns*
Care score of PBI *1,4							
>=42	915	433	47.3				
<42	734	357	48.6		*ns*		*ns*
Overprotection score of PBI *1,4							
<24	765	363	47.5				
>=24	889	426	47.9		*ns*		*ns*
Time to leaving home *1							
Early	701	417	59.5				
Late	913	366	40.1	0.45 (0.37-0.55)	*< 0.0001*	0.61 (0.47-0.79)	*< 0.001*
Time to returning home *1							
Early	783	320	40.9				
Late	848	473	55.8	1.83 (1.51-2.23)	*< 0.0001*	1.84 (1.45-2.34)	*< 0.0001*
Paternal factors							
Time to leaving home *1							
Early	551	302	54.8				
Late	933	401	43.0	0.62 (0.50-0.77)	*< 0.0001*		*ns*
Time to returning home *1							
Early	627	327	52.2				
Late	788	343	43.5	0.70 (0.57-0.87)	*< 0.01*		*ns*

*1 Categories were divided according to the median. *2 Relative risks approximated to odds ratio. CI denotes confidence intervals.
*3 Pittsburgh sleep quality index. *4 Parental bonding instrument.

likely to show problematic behavior (Yokomaku et al. 2008). However, our study is the first to use a survey with sleep questionnaires and the CBCL focusing on a number of preschool-age children. Our results showed that poor sleep habits were significantly related to behavioral problems; short sleep duration and irregular bedtime were significantly related to elevated attention problem scores and aggressive problem scores, although the effects were limited.

Short sleep duration and sleep disturbance have been associated with higher emotional lability in school-age children (Nixon et al. 2008; Rosen et al. 2004). Another study has also shown reduced attention, impaired school performance, and hyperactivity in children with sleep disorders (Gottlieb et al. 2004). Our results indicate that behavioral problems, such as attention problems, aggressive behavior, and depression/anxiety, were associated with deterioration of sleep habits even among a nonclinical sample of preschool-age children, as we had hypothesized.

The current study showed that sleep habits of 2- to 5-year-old children in Japan were poor; average bedtime on weeknights was later than 9:30 PM and average nocturnal sleep duration was less than 9.5 hours. Time in bed by parental report in a cohort of New Zealand Caucasian 7-year-old children was 10.9 hours (Nixon et al. 2008), which was similar to that reported in UK children (Gulliford et al. 1990). A U.S. national survey conducted in 2003 indicated that average bedtime on weeknights ranged from 8:44 PM at 2 years old to 8:58 PM at 5 years old, and the average sleep duration was 9.6 hours in 2- to 5-year-old children (National Sleep Foundation 2004). In comparison with these data, the results of our study demonstrated that sleep duration of the children was shorter, owing to the late bedtime. The nursery schools in this study routinely set a

Table 4. Results of univariate and multivariate logistic regression analyses of associated factors for children's irregular bedtime.

	Total	Irregular *1		Univariate Relative Risk (95% CI) *2	p	Multivariate Relative Risk (95% CI) *2	p
	n	n	%				
Maternal factors							
Bedtime *2							
Early	729	103	14.1				
Late	967	228	23.6	1.86 (1.44-2.41)	*< 0.0001*	1.58 (1.14-2.20)	*< 0.01*
Wakeup-time *2							
Early	745	103	13.8				
Late	955	228	23.9	1.96 (1.51-2.53)	*< 0.0001*		*ns*
PSQI *4							
< 6	1,149	198	17.2				
>= 6	516	127	24.6	1.56 (1.21-2.01)	*< 0.001*		*ns*
Care score of PBI *2,5							
>= 42	915	168	18.4				
< 42	734	151	20.6		*ns*		*ns*
Overprotection score of PBI *2,5							
< 24	765	131	17.1				
>= 24	889	190	21.4		*ns*		*ns*
Time to leaving home *2							
Early	701	103	14.7				
Late	913	209	22.9	1.72 (1.33-2.23)	*< 0.0001*	1.59 (1.13-2.23)	*< 0.01*
Time to returning home *2							
Early	783	154	19.7				
Late	848	162	19.1		*ns*		*ns*
Paternal factors							
Time to leaving home *2							
Early	551	99	18.0				
Late	933	175	18.8		*ns*		*ns*
Time to returning home *2							
Early	627	108	17.2				
Late	788	157	19.9		*ns*		*ns*

*1 Mother's description of their child's bedtime regularity is "irregular" or "moderately irregular". *2 Categories were divided according to the median. *3 Relative risks approximated to odds ratio. CI denotes confidence intervals. *4 Pittsburgh sleep quality index. *5 Parental bonding instrument.

nap schedule in the afternoon for children. The average nap duration in nursery schools was 2 hours for 2- to 3-year-old children and 1.5 hours for 4- to 5-year-old children. Therefore, differences in napping behavior were not thought to have a definitive influence in the present study. However, the long nap duration, especially in older children, might partially contribute to the nocturnal bedtime delay.

The current study found no significant association between the scale scores of the PBI evaluating care and overprotection by mothers and children's sleep habits. Of note, however, are that the late bedtime, short sleep duration, and irregular bedtime of children appeared to depend on the mother's daily schedule (i.e., wake-up time and time of returning home). The father's daily schedule had little or no effect on children's sleep habits. Our previous study also showed that mothers' sleep habits have a stronger influence on their children's sleep than fathers' sleep habits (Komada et al. 2009). These findings are due to the fact that the mother is still the main caregiver in Japan, suggesting that children's sleep habits are influenced more by the mother's schedule rather than her philosophy about how the children should be raised, as evaluated by the PBI. Therefore, our results emphasize the need for social support for mothers so that their burden can be reduced. This situation is different from that seen in some Western countries. There are smaller numbers of preschool-age children who sleep independently in Asian countries, although the National Sleep Foundation advises that children of all ages should fall asleep independently (Mindell et al. 2009). Considering this, differences in the relationship between sleep habits of children and that of parents according to country are needed.