Nocturnal wandering among cognitively impaired elderly inpatients in France

Cross-sectional and longitudinal analyses of predictors

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Background and Rationale

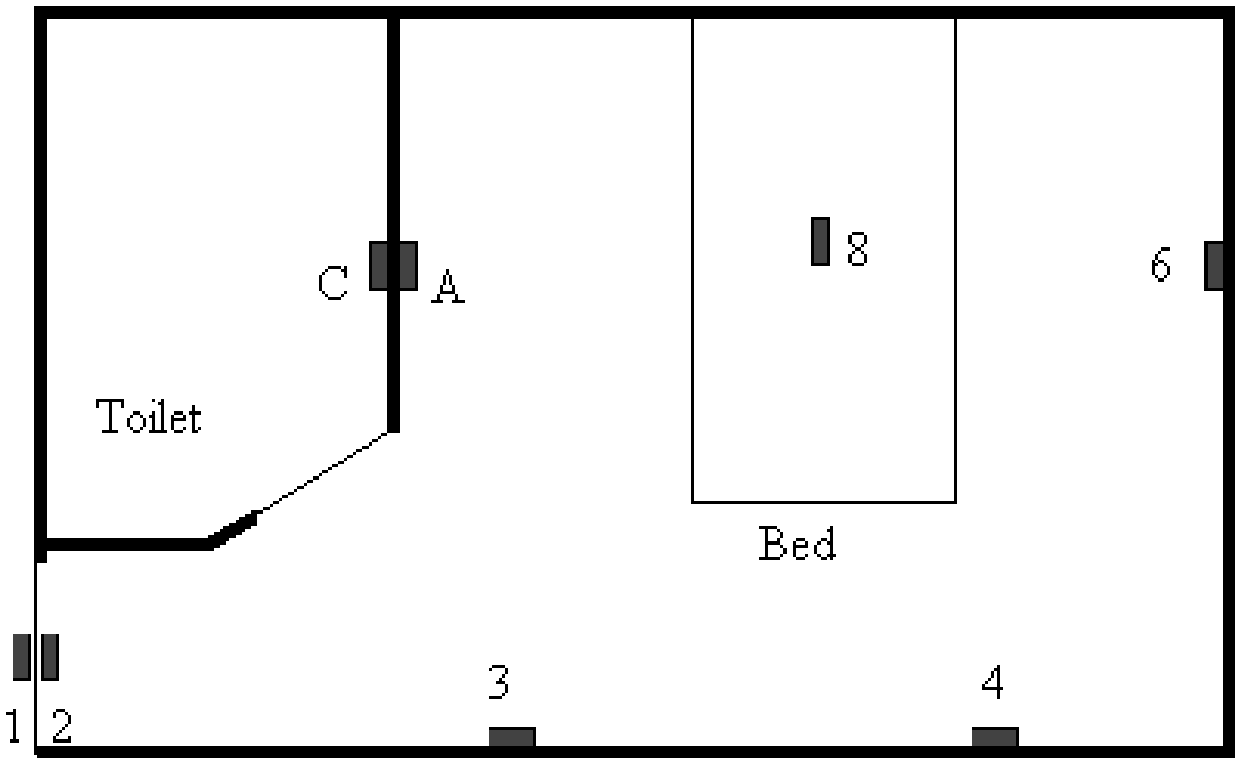
- Dementia, primarily characterised by progressive impairment of cognitive function, is more frequent at old age
- There is a rising trend in the number of old people
  - Implies a rise in the number of dementia cases
- One common behavioural problem in dementia is nocturnal wandering due to the inversion of sleep-wake rhythm
  - Nocturnal wandering is a burden to caregivers and family, and
  - The patient is at a greater risk to various other problems
- However, nocturnal activity is not often measured due to technical and financial difficulties
- In this context, a knowledge of the factors associated with nocturnal wandering could provide caregivers a better insight to the problem and improve patient management

Objectives

- Observe in a cross-sectional manner, if median nocturnal activity could be explained by clinically measured patient characteristics using standard tools for assessment
- Determine in a longitudinal manner, if there is a time-trend in nocturnal activity as well as to determine which patient characteristics could significantly predict nocturnal activity

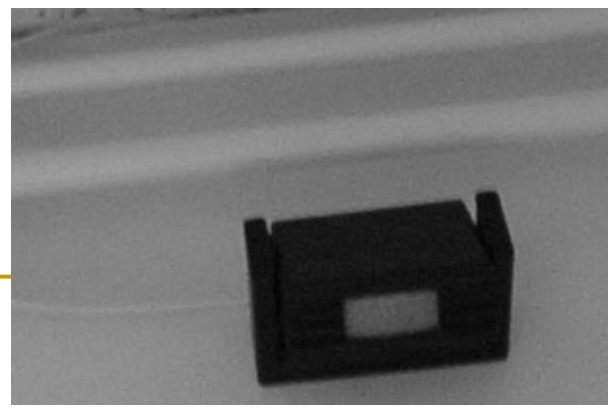
Methods: ‘smart’ patient bedroom

1		Wed May 02 22:02:26 2001
		Wed May 02 22:02:30 2001
1		Wed May 02 22:02:31 2001
12		Wed May 02 22:02:31 2001
2		Wed May 02 22:02:32 2001
23		Wed May 02 22:02:34 2001
3		Wed May 02 22:02:36 2001
3	A	Wed May 02 22:02:36 2001
	A	Wed May 02 22:02:37 2001
3	A	Wed May 02 22:02:38 2001
3		Wed May 02 22:02:40 2001
		Wed May 02 22:02:41 2001
3		Wed May 02 22:02:42 2001
23		Wed May 02 22:02:43 2001
2		Wed May 02 22:02:44 2001
12		Wed May 02 22:02:45 2001
1		Wed May 02 22:02:45 2001
		Wed May 02 22:02:47 2001
1		Wed May 02 22:02:48 2001
		Wed May 02 22:02:50 2001
1		Wed May 02 22:02:50 2001
		Wed May 02 22:02:51 2001
1		Wed May 02 22:02:54 2001
		Wed May 02 22:02:56 2001
1		Wed May 02 22:02:57 2001
		Wed May 02 22:02:59 2001
1		Wed May 02 22:03:02 2001
		Wed May 02 22:03:06 2001

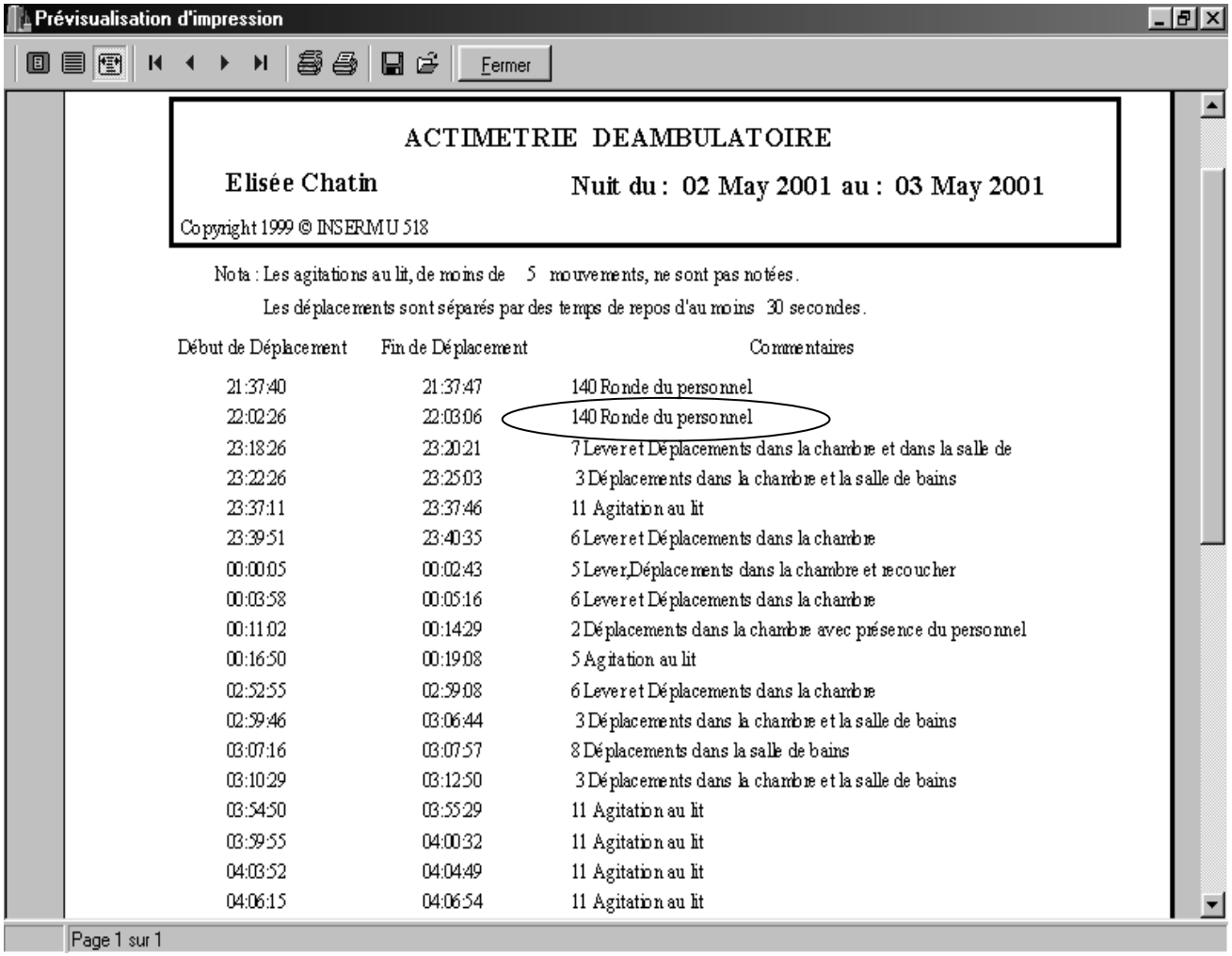


‘Visit by the personnel’ = excluded from analysis;

- Total 24 distinct types of movements identified,
- Classfied into 3 types: room, bed, toilet = total



Methods: G.A.R.D.I.E.N. report



Methods: patients & variables

- Inclusion criteria: patients admitted for ≥ 8 nights, of which ≥ 3 nights spent in the 'smart' bedroom for acclimatisation
- Exclusion criteria: patients who are immobile / bed-ridden, need support for displacements, have acute / severe illness, have fear of displacement
- Variables:
  - Exposure: cognitive function (MMSE, cut-off 24/25)
  - Covariates: autonomy (ADL, cut-off 3/4), immobility / frailty (Waterlow score, cut-off 10/11), depression (GDS, continuous)
  - Outcomes:
    1. Cross-sectional analysis: Median nocturnal activity (over 7 nights)
    2. Longitudinal analysis: Nocturnal activity (repeated measures over 8 nights)

    ☞ Total (= cumulative) nocturnal activity is measured over 6 hours (00:00-06:00)

Methods: statistical methods

- Cross-sectional analysis:
  - Log-transformed outcome approach (OLS)
  - GLM
    - Poisson distribution
    - Negative binomial distribution
- Longitudinal analysis:
  - Marginal (GEE) model
    - Poisson distribution
    - Negative binomial distribution
  - Hierarchical (GLMM) model
    - PQL method
    - Numerical method (adaptive Gaussian quadrature)
      - Poisson distribution
      - Negative binomial distribution
- Finite Mixture Model (of 'two' normal distributions):
  - Cross-sectional analysis: binomial distribution
  - Longitudinal analysis (marginal (GEE) model): binomial distribution

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Parts of the dataset

Exposure group & covariates | Outcome

	MMS_bin	GDS	Waterlow_bin	Median_activity_6hours	patid
1	1	13	1	9.33	2
2	1	15	1	7.23	3
3	1	14	1	10.95	4
4	0	4	1	3.23	7
5	1	14	0	45.48	8
6	0	20	1	0.00	9
7	1	15	1	1.08	10
8	0	14	1	1.65	11
9	1	23	1	5.60	12
10	0	19	1	2.65	13
11	1	12	0	19.62	14
12	1	6	0	67.97	15
13	0	7	1	3.95	16
14	1	7	1	9.38	18
15	1	17	1	19.70	19
16	1	14	1	3.18	20
17	1	25	1	0.78	21
18	1	15	0	10.57	23
19	1	11	0	71.92	24
20	1	22	0	2.10	25
21	1	5	1	48.30	27

Cross-sectional dataset

Exposure group | Outcome | Covariates

	Patid	Group	N1	N2	N3	N4	N5	N6	N7	N8	ADL_bin	GDS	Waterlow_bin
1	2	1	38	837	3153	981	560	263	136	567	1	13	1
2	3	1	434	0	645	508	526	296	137	411	0	15	1
3	4	1	730	281	1420	598	866	148	657	124	0	14	1
4	7	0	433	194	174	250	519	170	190	308	0	4	1
5	8	1	3820	4821	1475	1488	990	2729	6538	3493	0	14	0
6	9	0	0	1677	0	2354	1157	0	0	0	1	20	1
7	10	1	144	0	1013	65	799	0	0	72	1	15	1
8	11	0	0	51	170	175	99	108	0	197	0	14	1
9	12	1	0	4164	336	77	66	1173	1587	49	0	23	1
10	13	0	159	662	302	105	128	378	131	427	0	19	1
11	14	1	316	1177	1189	1222	383	544	1594	1127	0	12	0
12	15	1	4078	2005	3038	6640	4571	4066	4066	4066	0	6	0
13	16	0	296	252	31	237	562	145	136	953	0	7	1
14	18	1	459	455	867	563	1024	373	573	365	0	7	1
15	19	1	0	904	1640	1184	3575	1825	0	0	0	17	1
16	20	1	193	191	143	270	2891	0	0	905	0	14	1
17	21	1	0	58	28	1296	4934	47	0	640	0	25	1
18	23	1	698	423	823	681	566	634	522	211	0	15	0
19	24	1	3257	6636	6118	4894	1008	420	4315	5195	1	11	0
20	25	1	169	126	114	119	244	0	459	176	0	22	0
21	27	1	4475	2900	2600	5908	4320	2314	2246	3538	1	5	1

Longitudinal dataset – wide form

Results: demographic characteristics; N = 27

Characteristics	Exposure groups		*P*-values
	'Cognitively impaired' (MMSE ≥ 25) (N = 21)	**'Normal' cognitive function (MMSE < 25) (N = 6)**	
Age (years), mean (SD)	82.4 (6.0)	81.7 (7.2)	0.91
Men, N (%)	9 (43%)	2 (33%)	1.00
MMSE, mean (SD)	13.0 (5.2)	27.0 (1.3)	**< 0.01**
ADL, mean (SD)	4.0 (1.2)	4.8 (1.7)	0.16
IADL, mean (SD)	4.1 (4.2)	7.2 (4.6)	0.21
GDS, mean (SD)	14.2 (5.7)[1]	12.8 (7.1)[2]	0.77
Waterlow, mean (SD)	11.8 (3.7)	15.8 (4.5)	**0.05**
Hip / knee prosthesis, N (%)	2 (10%)	2 (33%)	0.20
Psychoactive medications, N (%)	20 (95%)	4 (67%)	0.11
Anti-dementia drugs, N (%)	13 (62%)	0 (0%)	**0.02**
Hypnotic / sedative drugs, N (%)	17 (81%)	4 (67%)	0.59
Antidepressants, N (%)	8 (38%)	3 (50%)	0.63
Neuroleptics, N (%)	13 (62%)	1 (17%)	0.08
Neoplasia, N (%)	2 (10%)	1 (17%)	0.54
Continent, N (%)	8 (38%)	5 (83%)	0.13
Presence of UTI / Diarrhoea, N (%)	2 (10%)	1 (17%)	0.54
Holter monitoring, N (%)	2 (10%)	0 (0%)	1.00
Extra-pyramidal signs, N (%)	7 (33%)	2 (33%)	1.00
Door barrier use at night, N (%)	6 (29%)	0 (0%)	0.28
Falls in the last six months, N (%)	14 (67%)	4 (67%)	1.00
Unable to get up after fall in the last six months, N (%)	12 (57%)	3 (50%)	1.00
Nocturnal activity (minutes), mean (SD)[3]	22.0 (21.3)	4.9 (3.3)	**0.01**

MMSE = Mini-Mental State Examination; ADL = Activities of Daily Living; IADL = Instrumental Activities of Daily Living; GDS = Geriatric Depression Scale; UTI = Urinary Tract Infection;
[1] N = 16; [2] N = 5; [3] Nocturnal activity averaged over 8 successive nights;
Continuous outcomes between the two groups were compared by Mann-Whitney-Wilcoxon test and binary outcomes between the two groups were compared by Fisher test.

Results: cross-sectional analysis; N = 21

(GLM: negative binomial model)

Parameters	Exponentiated estimates (95% CI)	*P*-values
Cognitive function MMSE < 25 MMSE ≥ 25	 6.12 (2.28-16.42) 1.0 (referent)	**< 0.01**
GDS (0-30)	0.88 (0.83-0.94)	**< 0.01**
Waterlow score > 10 ≤ 10	 0.38 (0.19-0.77) 1.0 (referent)	**< 0.01**
Dispersion parameter[1]	0.39 (0.08-0.71)	**< 0.01**

[1] Dispersion parameter (95% CI) is not exponentiated

Results: longitudinal analysis (1); N = 21

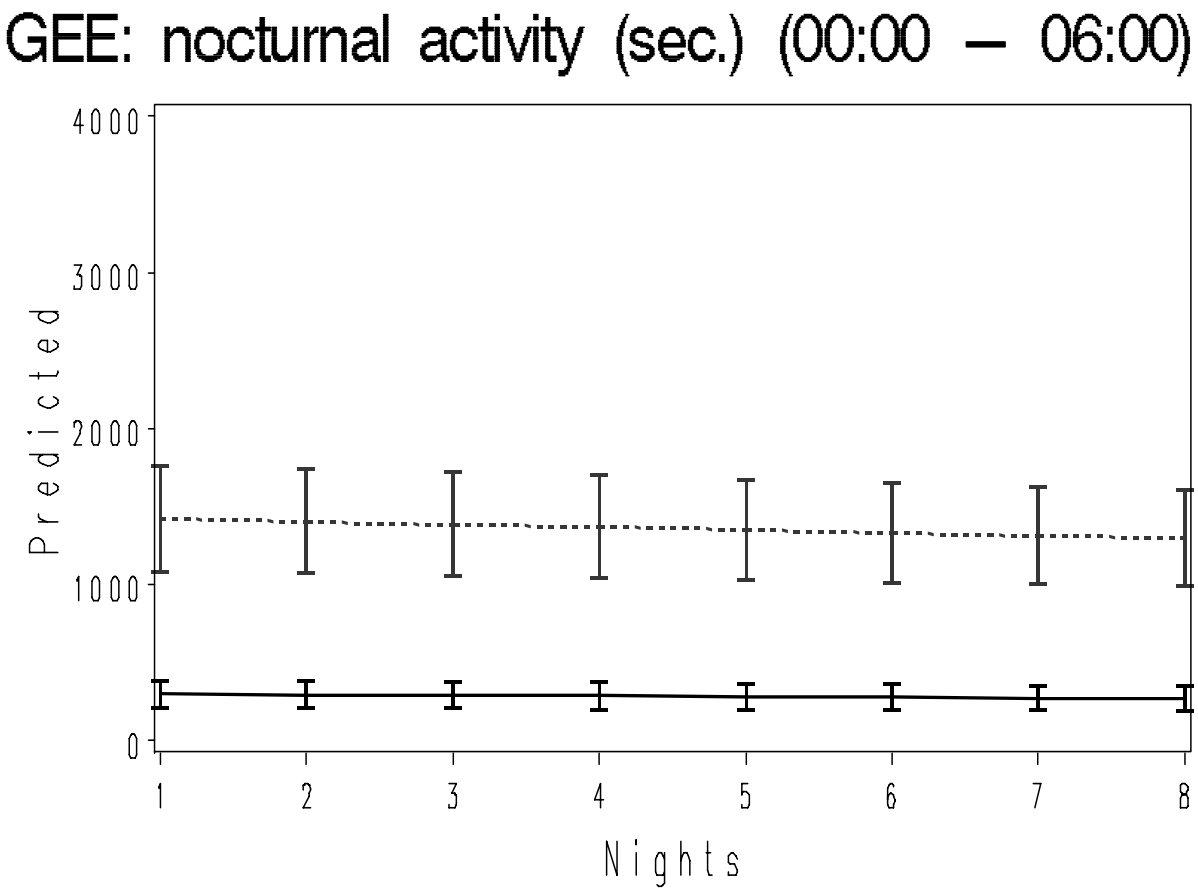
(GEE: negative binomial model, exchangeability assumption)

Parameters	Exponentiated estimates (95% CI)	*P*-values
Time (nights)	0.99 (0.94-1.03)	0.54
Cognitive function MMSE < 25 MMSE ≥ 25	 3.22 (2.11-4.90) 1.0 (referent)	**< 0.01**
ADL ≤ 3 > 3	 2.05 (1.13-3.72) 1.0 (referent)	**0.02**
Waterlow score > 10 ≤ 10	 0.49 (0.23-1.01) 1.0 (referent)	**0.05**
Dispersion parameter[1]	2.42 (2.00-2.84)	**< 0.01**

[1] Dispersion parameter (95% CI) is not exponentiated

Results: longitudinal analysis (2); N = 21

(GEE: negative binomial model, exchangeability assumption)



Cognitively impaired group (dotted); Normal cognitive function group (continuous) ± 95% CI

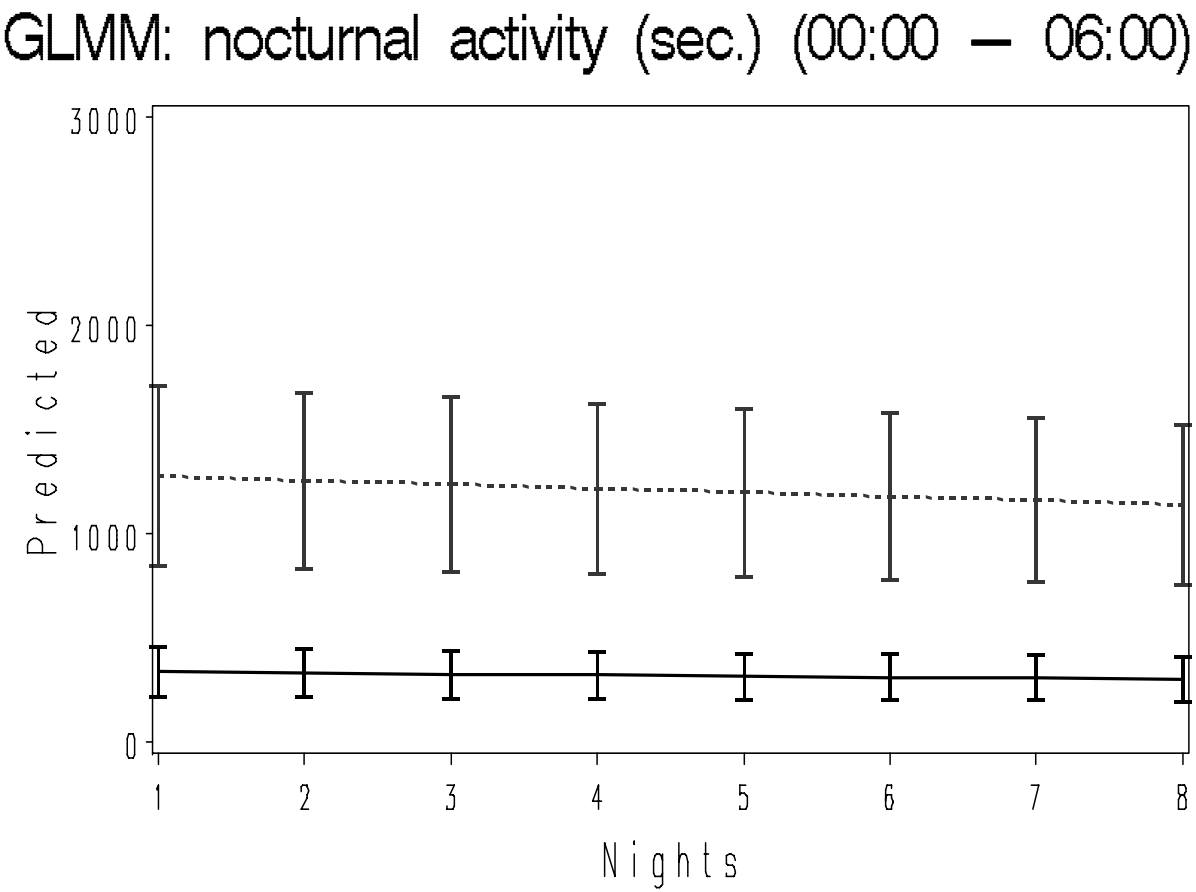
Results: longitudinal analysis (3); N = 21
(GLMM: negative binomial model)

Parameters	Exponentiated estimates (95% CI)	*P*-values
Fixed-effects estimates		
Time (nights)	0.98 (0.88-1.10)	0.76
Cognitive function MMSE < 25 MMSE ≥ 25	 3.38 (1.33-8.58) 1.0 (referent)	**0.01**
Random-effects estimates[1]		
Intercept variance	0.48 (0.00-0.96)	**0.05**
Dispersion parameter[1]	2.02 (1.57-2.47)	**< 0.01**

[1] Random-effects estimates (95% CI) and dispersion parameter (95% CI) are not exponentiated

Results: longitudinal analysis (4); N = 21

(GLMM: negative binomial model)



Cognitively impaired group (dotted); Normal cognitive function group (continuous) ± 95% CI

Discussion

- Globally impaired cognitive function was a significant predictor of increased nocturnal activity in cross-sectional & longitudinal analyses
- In cross-sectional analysis, low depressive mood & low immobility were associated with increased nocturnal activity in an elderly population having cognitive impairment of various degrees
- In longitudinal analysis, no effect of time or differential effect of time on exposure was observed; some residual between-subject variability was present
- Strengths:
  - Outcome measured by a robust, precise, validated system = objective measurement rather than subjective
  - Standard tools for measuring exposure and covariates
  - Very few missing data for the outcome variable (3%)
- Limitations:
  - Low statistical power (N = 21)
  - Missing covariate information for GDS in 22% subjects → patient exclusion
  - Generalisability issue (only inpatients)
  - Short duration of follow-up, without the initial phase, *i.e.*, more difficult to detect a significant time-trend

Acknowledgements

- To all patients and their family participating in this study
- To Pr. dr. Roel BRAEKERS for accepting to be the superviser and his valuable guidance
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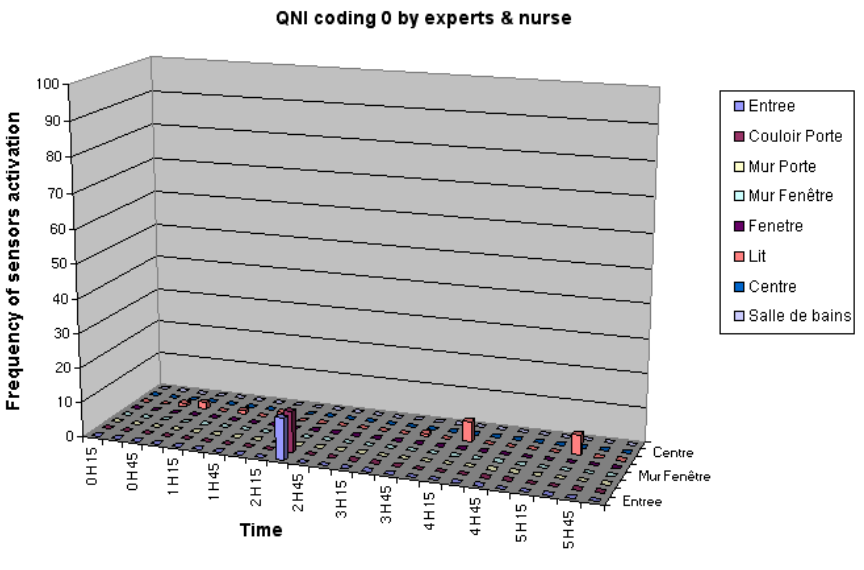
- To the France Alzheimer Association and AGRICA foundation for the financial aid in carrying out this study

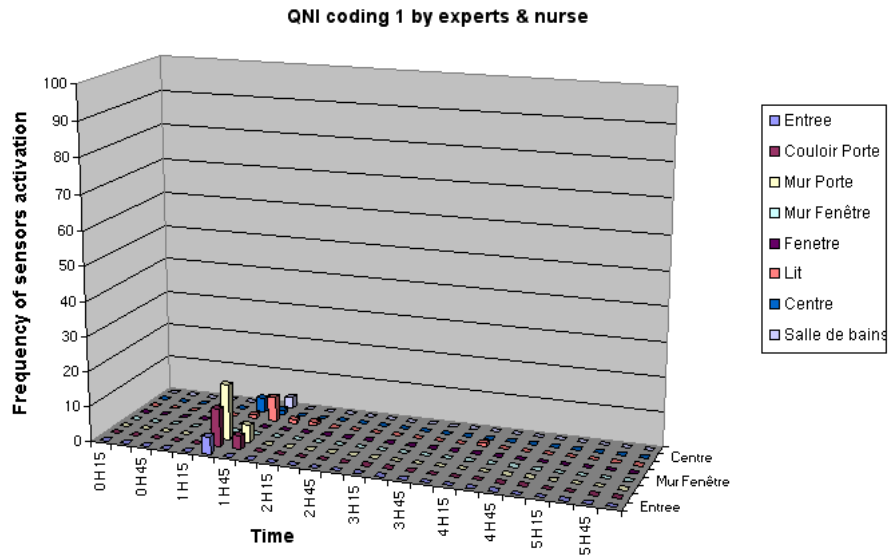
Back-up slides

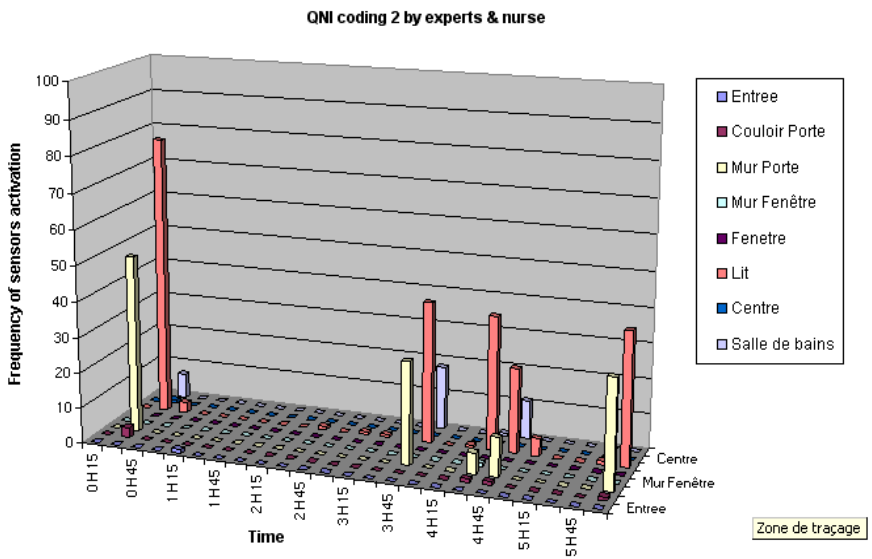
Future research

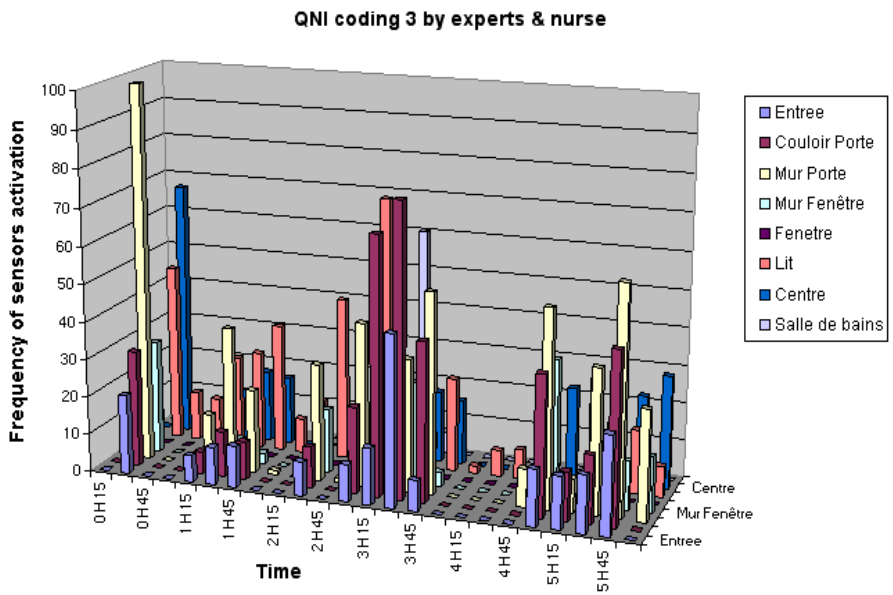
- More covariates, esp. those measuring psychomotor behaviour
- More subjects → more statistical power
- Longer follow-up, but at measured at non-contiguous time points (*e.g.*, 1 week apart), and the initial phase after admission need to be measured
- Easier questionnaires to administer in order to prevent missing covariate data
- Try other modelling approaches, *e.g.*, random splines, separate random-effects variance-covariance structures for each group, finite-mixture model for random-effects, Bayesian approach (Poisson-gamma mixture), recode data by removing filter, consider the 0 values as left-censored values, ...

Four levels of nocturnal activity: examples



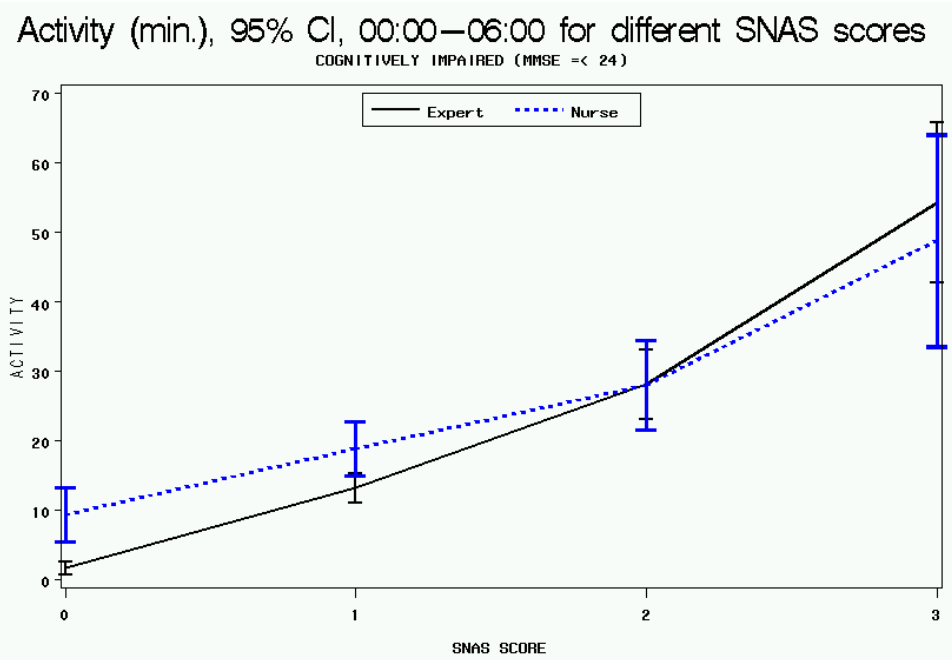






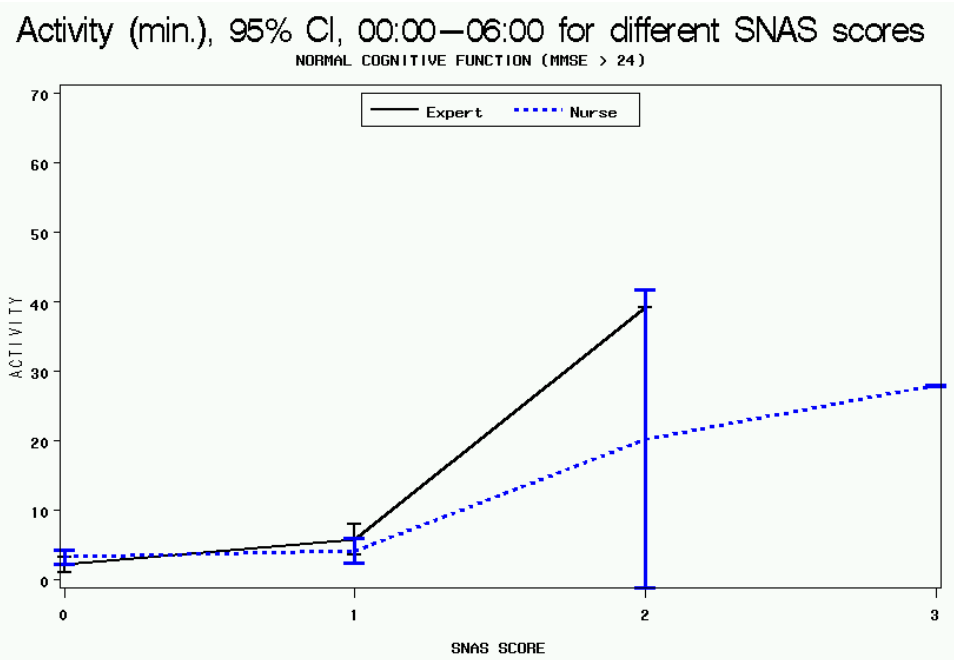
Comparison of two types of SUBJECTIVE assessments of nocturnal activity: expert vs. nurse

Cognitively impaired group



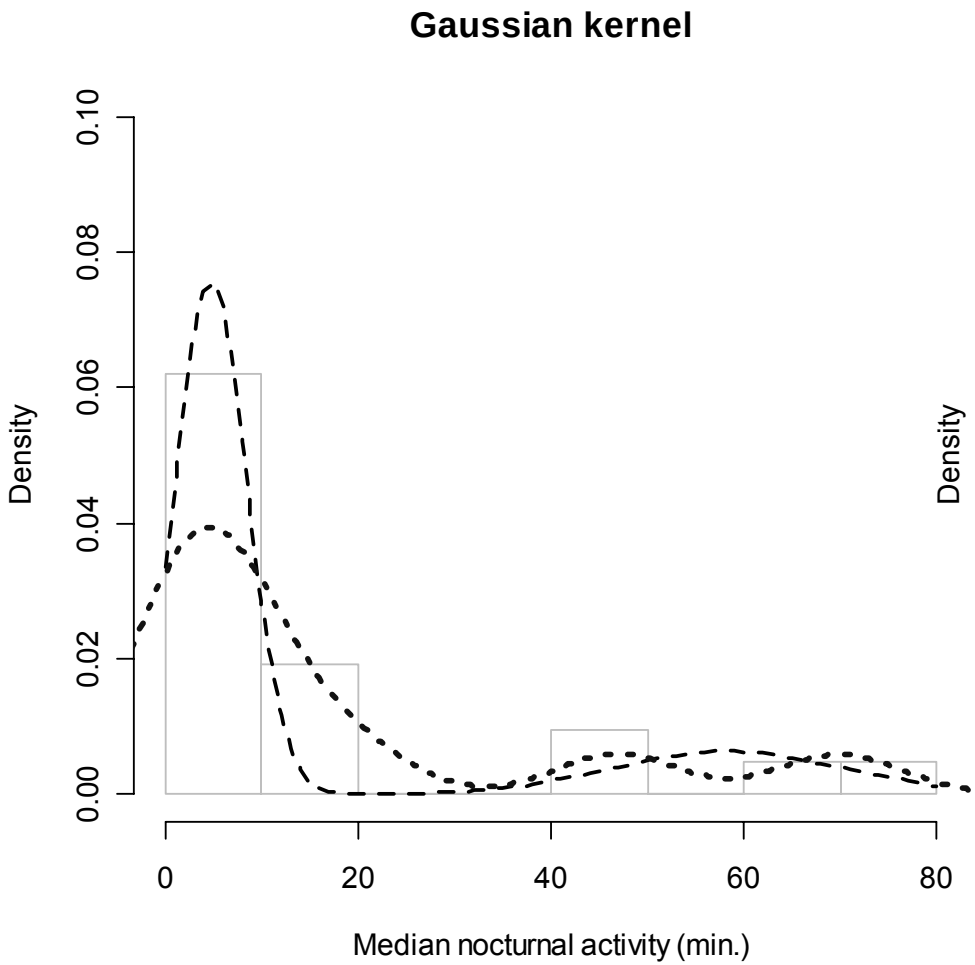
Weighted Cohen's kappa
= 0.45 (95% CI, 0.38-0.52)
i.e., moderate agreement
(No. of nights = 295)

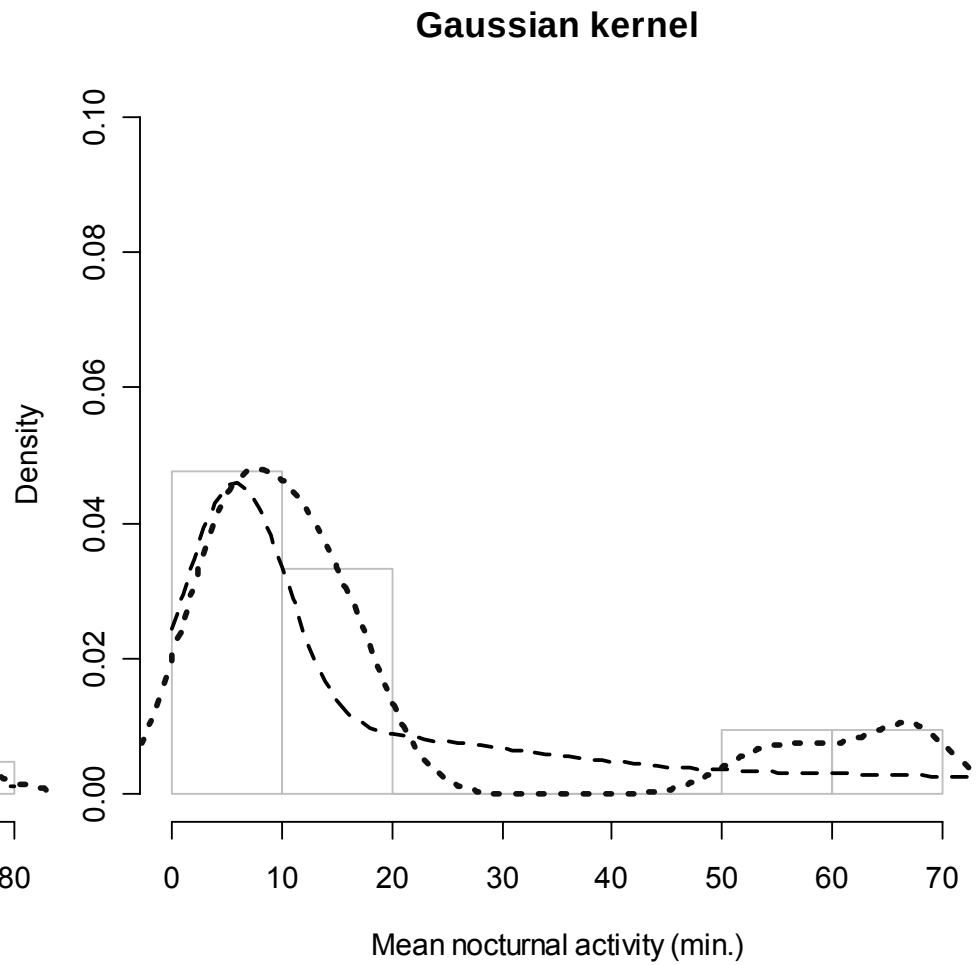
Normal cognitive function group



Weighted Cohen's kappa
= 0.27 (95% CI, 0.08-0.46)
i.e., fair agreement
(No. of nights = 57)

Finite mixture distributions; N = 21

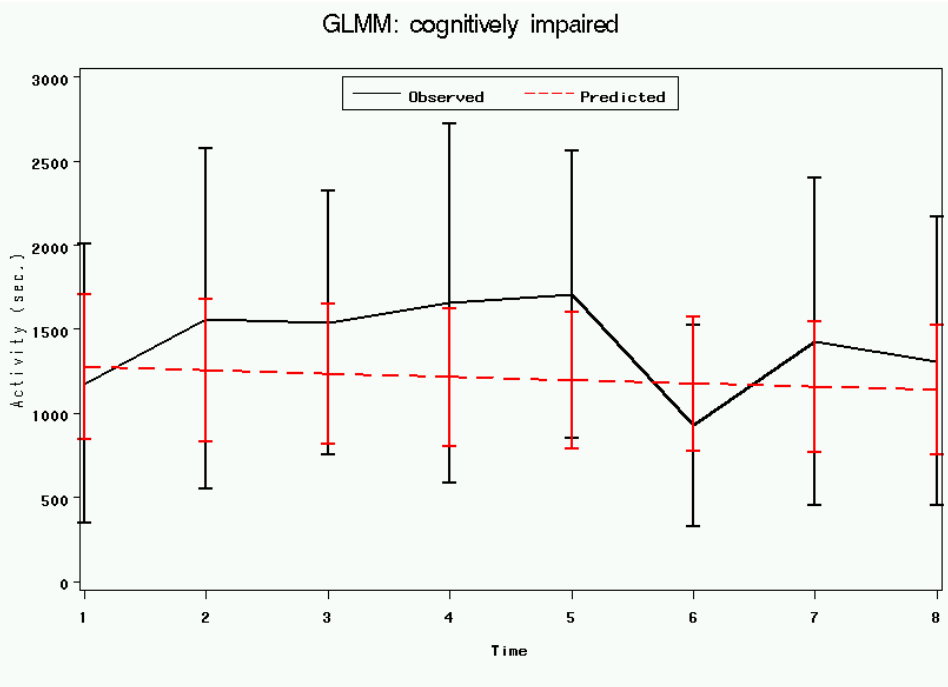


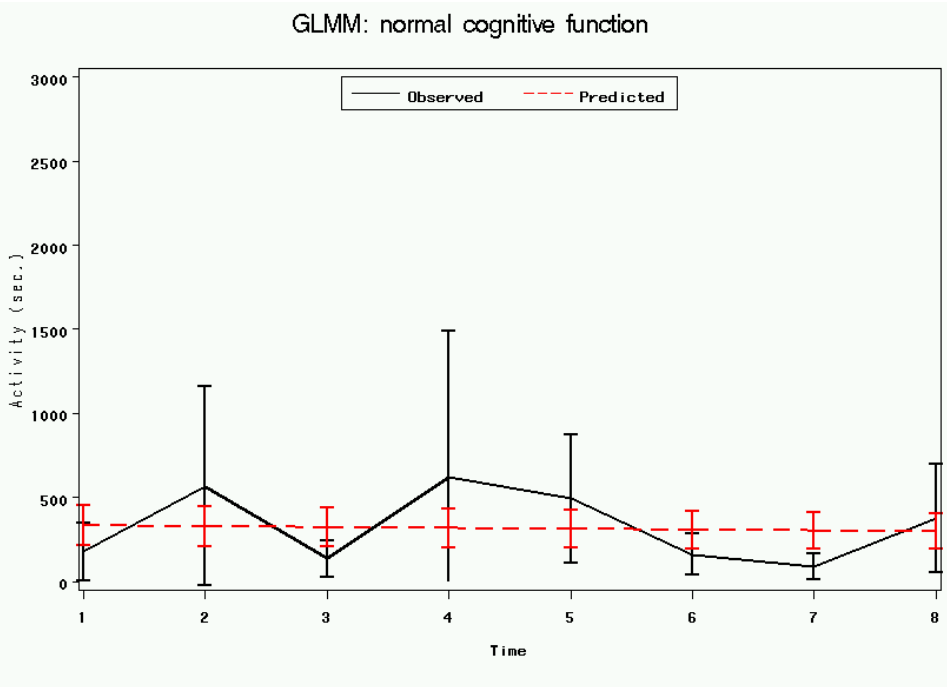


Median nocturnal activity (histogram) with dotted line (smoothing of the histogram), and dashed line (FMM).

Mean nocturnal activity (histogram) with dotted line (smoothing of the histogram), and dashed line (FMM taking into account the clustered nature of the data).

GLMM models: by exposure groups





Final random-effects (intercept) model

$$log[E(Y_{ij}|b_i)] = \beta_0 + \beta_1 X_{1i} + \beta_2 X_{2ij} + b_i$$
$$Y_{ij}|b_i \sim Negative\ Binomial(\lambda_{ij}, \varphi)$$
$$b_i \sim N(0, \tau^2)$$

Y_{ij} = outcome in subject i for measurement j
β_0 = mean outcome in 'normal' cognitive function group (*i.e.*, reference group)
β_1 = deviation in mean outcome of 'cognitively impaired' group from that of 'normal' cognitive function group
β_2 = slope of time variable
X_{1i} = known values of cognitive function variable in subject i
X_{2ij} = known values of time variable in subject i for measurement j
b_i = deviation in outcome of subject i from β_0 at baseline (*i.e.*, b_i is random-intercept of subject i)
τ^2 = variance of random-intercepts, *i.e.*, $var(b_i)$

Final random-effects (intercept) model: SAS code

GLMM: adaptive Gaussian quadrature

```
/*RANDOM INTERCEPT: NEGATIVE BINOMIAL MODEL*/
proc nlmixed data=ActimetryL qpoints=20 maxiter=50;
 parms int=5.811 T=-0.016 C=1.219 d11=0.481 k=2.017;
 eta=int+b1+T*time+C*category; /*linear predictor*/
 lambda=exp(eta);
 p=lambda/(lambda+1/k);
 ll=lgamma(activity+1/k)-lgamma(activity+1)-
    lgamma(1/k)+activity*log(p)+(1/k)*log(1-p);
 model activity~general(ll);
 random b1~normal(0,d11) subject=patid out=EB; /*Empirical Bayes estimate*/
 predict lambda out=nlmixedout_nb;
run;
/*'time x covariates' interactions are NOT significant (not shown)*/
```