Cognitive models of neurological disorders: the role of perceptual integration, decision-making and multiple memory systems

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Introduction

Characteristics clinical signs and symptoms of neurological disorders, such as multiple sclerosis (MS) and Parkinson's disease (PD), indicate the impairment of basic sensory and motor processes. However, recent evidence from cognitive neurology raised the possibility that fine-scale perceptual integration, decision-making, and multiple memory processes are also affected. In this series of studies, we investigated perceptual integration, contingency-dependent decision-making, stimulus-response (S-R) learning of sequences, and context representation in patients with MS, PD, and amnestic mild cognitive impairment (aMCI). We also assessed the effect of genetic traits related to PD on cognition in healthy volunteers.

MS is a common inflammatory disease of the central nervous system with genetic, environmental, and autoimmune causes, which eventually result in the loss of myelin, axons, and cortical atrophy. Cognitive and emotional disorders contribute to the psychosocial consequences of MS (quality of life, work activity, and social functions). Although visual deficits have obvious clinical implications, even MS patients with intact visual acuity and contrast sensitivity may demonstrate deficits, including slowed automatic visual information processing. Affective problems in MS can be modeled using tests of decision-making processes. The Iowa Gambling Test (IGT), which is sensitive to the lesions of the ventromedial prefrontal cortex, provides a unique opportunity to investigate special aspects of decision-making problems: hypersensitivity to reward, insensitivity to punishment, and "myopia for the future" when decisions are guided by immediate prospects instead of long-term outcomes of decisions.

PD accompanied by striatal dysfunctions is characterized by impaired skill and habit learning, whereas in Alzheimer's disease and aMCI, medial temporal lobe functions and explicit memory are more disrupted. The most frequently used experimental task to examine implicit learning in PD has been the serial reaction time task, which includes the learning of motor sequences. Dopaminergic mechanisms in the striatum are involved in the learning of sequential ("chaining") S-R associations, in which each link in a sequence of stimuli leading to reward is trained step-by-step using feedback after each decision, until the complete sequence is learned. In PD, cellular death in the substantia nigra pars compacta leads to the depletion of dopamine in the striatum In addition to the motor symptoms, dopaminergic loss in the striatum results in a variety of cognitive dysfunctions, with a special reference to habit and skill learning, which is based on trial-by-error choices, feedback, and reward. Based on

the assumptions outlined above on the relationship between sequence learning and dopamine, it is possible that the genetic variation of the alpha-synuclein (ASN) gene may be related to this type of learning. ASN, which is a key component of Lewy-bodies, is predominantly localized in the presynaptic terminal of the neurons as a molecular chaperone in the SNARE complex, which regulates neurotransmitter release, vesicle recycling, synaptic plasticity, and neuronal survival. ASN is especially prevalent in dopaminergic neurons and influences the release of the transmitter. It may be directly related to the regulation of the reward prediction function of dopamine, given that the decreased expression of the ASN gene results in the sensitization of the reward system and leads to significantly altered operant behavior.

Aims and hypotheses

1. Highly functioning MS patients without visual complaints show subtle abnormalities in perceptual integration, which is mediated by lateral connections in the primary visual cortex.
2. Affective problems in MS can be modeled using tests of decision-making processes. For such purposes, we used the IGT, which is sensitive to the lesions of the ventromedial prefrontal cortex.
3. In a combined S-R sequence learning and context representation test, PD patients with basal ganglia dysfunctions show impairments in the S-R learning phase, whereas aMCI patients with medial temporal lobe pathology show relatively intact learning.
4. The S-R learning deficit is related to risk PD variants of the ASN gene.

Materials and methods

I. Visual integration in MS

Twenty-two young, visually unimpaired MS patients with minimal symptoms and thirty healthy controls subjects participated in the study. Expanded Disability Status Scale (EDSS) (Kurtzke, 1983) scores less than 2, less than 5 years since diagnosis, no evidence for visual impairments as measured with the 25-item National Eye Institute Visual Function Questionnaire (VFQ-25), Beck Depression Inventory (BDI) scores less than 10, and the absence of other neurological, ophthalmologic, and psychiatric disorders.

During the *flanker task* the computer-generated stimulus field consisted of three Gabor patches presented against a uniform gray background. The vertically or horizontally oriented target Gabor patch was flanked with two lateral Gabor patches. The contrast of the target was 8%, whereas that of the flankers was 40%. The spatial frequency was 6.7 cycles/degree. The center-to-center distance between target and flankers was 4λ. First, participants were asked to press the space button on the computer keyboard. After this, a fixation display of 500-ms appeared. A central cross indicated the location of the subsequent target. After the fixation display, an interval of 40-, 60-, 80-, or 100-ms appeared during which the stimulus display was presented. Participants were asked to indicate whether the orientation of the target was vertical or horizontal pressing separate buttons on the computer keyboard (‘‘1’’ and ‘‘9’’). Ten trials were administered at each exposure time. Performance was defined as the proportion of correctly detected target stimuli. *Background neuropsychology* included digit span forward and backward, Symbol Digit Modalities Test, verbal (FAS) fluency, and California Verbal Learning Test-II.

II. Decision-making in MS

Twenty-one outpatients with relapsing-remitting MS and 30 matched healthy control volunteers participated in the study. The Expanded Disability Status Scale (EDSS) (Kurtzke, 1983) scores were 0 in the case of 3 patients, 1 in the case of 3 patients, 2 in the case of 13 patients, and 3 in the case of 2 patients (mean: 1.7). *Background neuropsychology* included Wisconsin Card Sorting Test (concept formation and attentional set-shifting), Digit Span Forward and Backward (attention and short-term memory), Symbol Digit Modalities Test (speed of information processing and divided attention), Verbal Fluency (selection and retrieval of linguistic material). During the IGT, contingency learning based on the cumulative effect of reward and punishment was assessed. In the ABCD version, advantageous decks are characterized by immediate small reward but even smaller future punishment. In the EFGH version, advantageous decks are characterized by immediate large punishment but even larger future reward.

III. Chaining association in PD, aMCI and the effect of the ASN gene

Twenty healthy controls, fourteen patients with aMCI, and sixteen never medicated-patients with PD (Hoehn-Yahr stages: I–IV, median: 2.8) participated in the study. All subjects received background neuropsychological testing including verbal IQ, Mini-Mental State Examination (MMSE), Rey Auditory Verbal Learning Test (RAVLT), Boston Naming

Test (BNT), and semantic fluency (SF) test. During the *chaining association task*, the subject's task is to guide an animated character through the rooms, to a goal point, the outside world. In the training phase, each link in a sequence of stimuli leading to reward is trained step-by-step using feedback after each decision, until the complete sequence is learned. In the probe phase, the context of S-R associations must be used (the position of the associations in the sequence).

To test the effect of ASN polymorphism on chaining associative learning 204 healthy volunteers were genotyped. Genomic DNA was extracted from venous blood samples. Ten SNPs in the 30-region (block B) of ASN gene were genotyped (rs356180, rs356169, rs2572323, rs356219, rs356220, rs356165, rs356204, rs3822086, rs356203 and rs356168). These SNPs show linkage disequilibrium and previously six haplotypes were identified (Mueller et al. 2005). Four of these haplotypes (TAGACAGCAT, CAGACAGCAT, CCGACAACAC and CAGACAACAC) are associated with decreased risk of PD, and two of the six haplotypes (TCAGTGACGC and CAGGTGATGC) are associated with increased risk of PD. Genotyping was performed using the matrix-assisted laser desorption/ionization time of flight (MALDI-TOF) mass spectrometry.

Results

I. Visual integration and speed in MS

The results revealed that the controls performed better when collinear flankers were presented [$F(1,50)=5.33$, $p<0.05$], similarly to the patients [$F(1,50)=17.89$, $p<0.001$]. Critically, the 3-way interaction between group, flanker orientation, and exposure time was significant [$F(3,150)=5.16$, $p<0.005$], suggesting that the difference between the patients and the controls was influenced by both flanker orientation and exposure time. Tukey HSD tests indicated significantly lower orientation detection performances in the patient group as compared with the control group in the orthogonal condition at 40-ms exposure time ($p<0.01$), whereas the other comparisons did not reveal statistically significant between-group differences ($p>0.1$) . In the critical orthogonal condition at 40-ms exposure time, 18 of the 22 multiple sclerosis patients (81.8%) performed below the 95% confidence interval of the control mean. The confidence intervals of the patients and controls did not overlap. The controls responded faster when collinear flankers were presented [$F(1,46)=21.40$, $p<0.001$], similarly to the patients [$F(1,46)=6.32$, $p<0.01$]. The interaction between group and exposure

time was significant [$F(3,138)=3.46$, $p<0.05$], but the post hoc tests revealed no significant between-group differences ($p>0.05$). The remaining interactions did not reach the level of statistical significance ($p>0.2$). An analysis of linear trend revealed a significant group by exposure time interaction [$F(1,48)=4.3$, $p<0.05$]. Although the controls showed decreasing reaction time along with increasing exposure time in both collinear and orthogonal conditions ($p<0.05$), the patients did so in neither condition ($p>0.5$).

II. Decision-making in MS

The MS patients made significantly less advantageous decisions than the controls in the ABCD task after 1–20 [$t(49)= -3.28$, $p< 0.01$; power= 0.41], 41– 60 [$t(49)= -2.01$, $p< 0.05$; power=0.51], 61–80 [$t(49)= -4.40$, $p< .001$; power>0.9], and 81–100 trials [$t(49)=-4.22$, $p<0.001$; power>0.9]. Similar differences were found in the EFGH task after 41– 60 [$t(49) = -2.57$, $p< .05$; power= 0.66], 61–80 [$t(49)= -4.55$, $p< .001$; power> 0.9], and 81–100 trials [$t(49)= -4.99$, $p< 0.001$; power>0.9]. The linear regression analysis revealed that the WCST perseverative errors, digit span, symbol digit, and verbal fluency scores did not predict ABCD and EFGH task performances after 100 trials ($p>0.4$).

III. Chaining associations in PD and aMCI

The background neuropsychological testing indicated characteristic cognitive impairments in aMCI. The ANOVA conducted on the number of errors in the four training phases of the chaining task revealed a significant main effect of group ($F(1,42)=8.87$, $p<0.001$) and training phases ($F(3,126)=11.30$, $p<0.0001$). The interaction between group and training phases was significant ($F(6,126)=3.75$, $p<0.01$). However, this interaction was not significant when controls were compared with patients with aMCI using an F-test for linear trend ($p = 0.4$). In contrast, the group by training block interaction was significant when controls were compared with patients with PD ($F(1,42)=13.04$, $p<0.001$) and when patients with aMCI were compared with patients with PD ($F(1,42)=14.63$, $p<0.001$). Tukey's HSD tests confirmed that patients with PD were impaired in this phase of the chaining task as compared with controls ($p<0.01$) and with patients with aMCI ($p <0.005$). According to the Tukey's HSD tests conducted on the group by training phase interaction, this difference was significant only in the fourth training phase ($p<0.005$). Control subjects and patients with aMCI did not differ.

The ANOVA conducted on the number of errors in the context-dependent probe phase revealed a significant main effect of group ($F(1,42)=6.75$, $p<0.01$). Tukey's HSD tests

revealed that patients with aMCI committed more errors than controls ($p<0.05$) and than patients with PD ($p<0.005$). Control subjects and patients with PD did not differ ($p>0.4$).

IV. ASN and chaining associative learning

Participants with 3'-block risk haplotypes committed more cumulative errors during the training phase (mean number of errors: 2.3, SD=1.7) compared with participants carrying protective haplotypes (mean number of errors: 1.6, SD=0.8) [$t(199)=-3.81$, $p<0.001$]. As the length of the sequence increased (from phase 1 to phase 4), the mean number of errors also increased [main effect of phase: $F(3,597)= 20.96$, $p<0.001$]. The effect of haplotypes was also significant [$F(1,199)= 14.55$, $p<0.001$]. Participants with risk haplotypes committed more errors in phases 2, 3 and 4 compared with participants carrying protective haplotypes ($t>2.4$, $p<0.05$). In the probe phase, participants with protective haplotypes performed worse (mean number of errors: 2.3, SD= 2.6) than participants with risk haplotypes (mean number of errors: 1.5, SD= 2.0) [$t(195)=2.30$, $p<0.05$; ANOVA interaction between haplotypes (protective vs. risk) and task phase (training vs. probe): $F(1,195)=14.74$, $p<0.001$). The percentage of chaining errors was 70.5% (SD=58.6) in the case of participants with risk haplotypes, whereas this value was 81.9% (SD=47.4) in the case of participants with protective haplotypes ($p>0.1$). Participants with protective and risk haplotypes did not differ in WCST, verbal fluency, mirror reading and pursuit rotor.

DISCUSSION

The results of this series of studies in MS, PD, and aMCI revealed a unique pattern of cognitive task performance in these patients, which can be interpreted in parallel with the critical neuronal structures affected in these disorders. First, contrary to our hypothesis, we did not find perceptual integration deficits in patients with MS, which is against the hypothesis of impaired lateral connections in early visual areas. However, patients with MS showed significantly slowed visual information processing, which was confined to the orthogonal flanker condition at the shortest exposure time. Second, we demonstrated signifcantly altered decision-making in MS in both reward- and punishment-guided conditions, which may indicate the impairment of emotion-related brain areas such as ventromedial prefrontal cortex, insula, and amygdala. Third, unmedicated patients with PD displayed impaired chaining associative learning performance, which can be explained by dysfunctional feedback-prediction processing in the basal ganglia. Patients with aMCI

displayed the opposite pattern of performance with relatively sufficient chaining learning and impaired context representation, which may point at a deficit of the medial temporal lobe. Finally, and perhaps most interestingly, the PD risk haplotype of the ASN gene was associated with a lower efficacy of chaining learning relative to the protective haplotype, which is consistent with the results obtained in PD and may indicate a genetic background of impaired feedback processing.

The data from young MS with mild symptoms, low level of depression and fatigue, spared VEP, contrast sensitivity, and neuropsychological performance showed robust and selective impairments in the orientation detection task; in the orthogonal condition at short exposure time (40-ms), their performance remained below the 50% chance level. The spared VEP and visual contrast sensitivity are against the demyelinating pathology of the foveal retino-cortical pathway in this sample, and therefore the deficit uncovered by the flanker task cannot be detected by conventional clinical methods. In young, non-depressed, relatively highly functioning patients with MS, we also found impaired decision-making on the ABCD and EFGH versions of the IGT. The difference between patients and controls was more pronounced in the later phase of test, which suggests that poor decision-making is a consequence of impaired learning across trials and not of generalized cognitive impairments. Although executive dysfunction is characteristic for MS and may contribute to impaired IGT performances, in our study it was not associated with IGT performances. According to our results, patients with MS show a similar performance to that found in patients with ventromedial prefrontal damage: their decisions are guided by recent outcomes irrespective of gain or loss.

Our results are consistent with the view that patients with PD show substantial learning deficits on tasks requiring trial-by-error, feedback-based stimulus-response learning, especially when sequences or chains of associations must be acquired. In contrast to the patients with PD, patients with aMCI exhibited intact learning on the training phase of the chaining task. In general, patients with aMCI exhibit prominent episodic memory impairment, and sophisticated neuroimaging and neuropsychological methods reveal subtle alterations in medial temporal lobe. The most interesting finding was that, in contrast to patients with PD who exhibited normal performance during the context-dependent probe phase of the chaining task, patients with aMCI committed significantly more probe errors than controls. The probe phase was intended to verify that participants had learned the correct door in its correct place in the sequence, encoding not only the correct door but also its context (the room in which it

occurred). The deficit of context representation in aMCI is consistent with medial temporal lobe dysfunction.

The data suggest a double dissociation between stimulus-reward and context-dependent cognitive sequence learning in participants with risk and protective haplotypes of ASN associated with PD. Because L-DOPA improved stimulus-reward learning of chaining sequences in patients with PD, it is plausible to hypothesize that the risk haplotypes of ASN are associated with decreased dopaminergic transmission and reward signal in the basal ganglia, which is consistent with animal models. Further studies are warranted to explore how polymorphisms of PD-associated genes affect these processes, as potential biomarkers of early diagnosis.

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Papers related to the thesis

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