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Attentional ability among survivors of leukaemia

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Abstract

Attentional ability in 19 survivors of acute lymphoblastic leukaemia and 19 sibling controls was assessed using a neuropsychological model of attention. Analysis revealed that children who had received treatment for leukaemia exhibited significantly poorer performance on measures of the "focus encode" and "focus execute" elements of attention and on measures of the ability to respond to external cues and feedback. No significant differences in performance were found for measures of sustained attention and the ability to shift attention. These results indicate that children who have received treatment for leukaemia may experience highly specific attentional deficits that could have an impact on academic performance, particularly mathematical and reading skills. It is suggested that this underlying attentional deficit might be the source of the neuropsychological sequelae associated with the disease. Future attempts at remediation should incorporate activities specifically designed to ameliorate focusing difficulties.

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Children receiving treatment for acute lymphoblastic leukaemia (ALL) may experience intellectual deficits,[1 2] and it has become clear that the possibility of cognitive dysfunction among survivors of childhood ALL needs to be investigated.

Early studies tended to concentrate on confirming the existence of neuropsychological sequelae among children treated for ALL.[3–5] However, as more evidence emerged it became apparent that particular aspects of cognitive functioning were repeatedly reported as problematic—for example, attentional ability,[6–10] memory,[10–12] mathematical ability,[13–15] abstract reasoning,[16 17] and verbal ability.[18 19] The underlying source of these deficits remains unclear.

The process of attention can be viewed as the building block for other more complex forms of cognitive activity and it has been suggested that difficulties in higher order cognitive processes, such as memory, reasoning, and mathematics may result from an underlying deficit in the ability to sustain attention.[10] However, much previous research investigating attentional ability in ALL has studied only certain aspects of attention such as reaction times or "freedom from distractibility",[7] making it difficult to support Brouwers *et al*'s assertion that specific difficulties in sustaining attention are at the core of the cognitive difficulties witnessed among the childhood leukaemia population.[6] To gain a more detailed picture of the exact nature of any attentional problems experienced by survivors of childhood leukaemia we adopted a model of attention which considers the subcomponents that comprise this cognitive process.[20]

Mirsky *et al* delineated attention into three elements: focus, sustain, and shift.[20] The focus element of attention can be further subdivided into "focus encode" and "focus execute". Focus encode requires the individual to target, recall, and then manipulate information. Focus execute refers to the ability to target information rapidly and efficiently and then make a subsequent response based on that information. The sustain element is the capacity of the individual to maintain focus over a period of time: to maintain alertness or vigilance. Shift refers to the ability of the individual to change the focus of attention in an adaptive and flexible manner. This model of attention was selected for a number of reasons. First, the factorial approach facilitates a systematic approach to the study of attentional ability. Second, the model provides suggestions as to the localisation of function within the brain of the differing attentional factors, which it is hoped will provide insight into the specific nature of any brain damage experienced by these patients. Finally, there is a growing body of evidence that provides empirical support for the model.[21–23] However, we acknowledge the theoretical nature of the model and advise caution in the interpretation of our results.

We have attempted to gain an insight into attentional ability among a cohort of children in complete continuous remission from ALL through the adoption of the model of attention described earlier. We used tasks that are believed to yield information regarding the individual elements of attention, with the aim of providing a detailed analysis of attentional ability among this group of patients.

Participants and methods

We studied 19 children in long term remission from ALL with nineteen sibling controls. Of the children with ALL, three had received treatment protocol UKALL VIII and the remainder had received UKALL X. All had received 18 Gy cranial irradiation (CRT) and intrathecal methotrexate (ITMTX) and had stopped treatment at least two years previously. The treatment protocols differed in timing and length of intensification. Children in the UKALL VIII protocol received CRT in 10 sessions over 12 days and received six or seven doses of ITMTX. The UKALL X group also received 18 Gy CRT but were randomised to

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Table 1 Age at diagnosis and at assessment, and sex of participants in the leukaemia group and their sibling controls

Group	*Male*	*Female*	*Age at diagnosis (months) range (mean)*	*Age at testing (months) range (mean)*
Leukaemia	9	10	20–86 (44.89)	90–184 (130.58)
Siblings	7	12	Not applicable	89–188 (134.3)

Table 2 The attentional process, showing the appropriate test for each element

Focus encode	*Focus execute*	*Sustain*	*Shift*
Arithmetic (WISC-R)	Speed of information processing (BAS)	VIGIL	Wisconsin card
Digit span (WISC-R)	Coding (WISC-R)		Sorting test

treatment groups that received either six, seven, or eight doses of ITMTX. Other differences within the UKALL X cohort were as follows:

Group A: identical to UKALL VIII
Group B: early intensification at week 5
Group C: late intensification at week 20
Group D: both intensifications.

Radiotherapy was always given within three months of diagnosis. Further details are given in table 1.

Each child received the following tests:

(1) Arithmetic subtest of the Weschler intelligence scale for children (revised) (WISC-R)[24]
(2) The digit span subtest of the WISC-R
(3) The speed of information processing subtest of the British ability scales (BAS)[25]
(4) The coding subtest of the WISC-R
(5) VIGIL[26]
(6) The Wisconsin card sorting test (WCST).[27]

Table 2 gives details of which tests were used for the various elements of the attentional process.

THE FOCUS ELEMENTS OF ATTENTION

We used the arithmetic and digit span subtests to examine the focus encode elements of attention. They require sequential registration and mental manipulation of information.

The digit span subtest involved the verbal presentation of lists of up to nine digits at the rate of one digit each second. We asked subjects to recall all of the numbers in the lists either in the order of presentation or in reverse order.

The arithmetic subtest involved verbal presentation of mathematical problems. We asked subjects to calculate the answers to the problems without the use of pen or paper and within a specific time limit.

The speed of information subtest and the coding subtest examine the focus execute element of attention. They require the scanning of stimuli to locate a target efficiently and quickly and then the execution of a rapid skilled manual response.

During the speed of information processing subtest we presented subjects with a booklet containing 10 pages, each displaying three or four rows of numbers. We asked the subjects to draw a line through the largest number in each row as quickly as possible.

The coding subtest required subjects to fill in blank squares with specific symbols as quickly as possible according to the code provided at the top of the page.

All of these tests are commonly used to assess orienting and attentional skills[28] and freedom from distractibility,[29] and are believed by Mirsky and colleagues[20] to be appropriate methods of assessing this aspect of performance.

THE SUSTAIN ELEMENT OF ATTENTION

In their original paper, Mirsky and colleagues[20] suggest using the continuous performance task (CPT) originally developed by Rosvold and colleagues[30] as a measure of sustained attention or vigilance. We used the VIGIL test battery instead of the CPT for a number of reasons. We considered that the age of the participants suggested that a requirement to sustain attention for seven minutes was more appropriate than the lengthier requirements of the CPT (up to 14 minutes). Secondly, VIGIL provides the examiner with substantially more information than the CPT, including information regarding false alarms and omissions. In addition, VIGIL enables the examiner to compare performance across four blocks of trials in terms of reaction time, number of commissions, and number of omissions. Participants cannot detect these four blocks. This information can help to determine any changes in concentration over time and how these changes may affect reaction time, successful detection of target stimuli, and impulsivity. We presented subjects with computer generated letters which flashed on to the screen, with an interstimulus interval of 900 ms. Subjects were required to press the space bar each time they saw the letter "K".

THE SHIFT ELEMENT OF ATTENTION

Following Mirsky *et al*,[20] we used the WCST to examine the shift aspect of attention. The test requires subjects to apply reasoning ability and change cognitive strategies in response to a changing environment. The WCST consists of four stimulus cards and 128 response cards that depict figures of various forms (crosses, circles, triangles, or stars), colours (red, blue, yellow, and green), and numbers of figures (one, two, three, or four). The four stimulus cards were placed from left to right in the following order:

one red triangle	two green stars	three yellow crosses	four blue circles

Subjects were given the pack of response cards and asked to match each consecutive card from the pack with one of the stimulus cards. Participants were told whether their response was correct or not but they were not told the correct sorting principles. When the participant had made 10 consecutively correct responses the sorting principle would be changed without warning and the participant was required to rely on the examiner's feedback to determine the new sorting principle. Further support for the use of this measure as an appropriate tool for the assessment of the ability to respond flexibly and strategically to a changing environment can be found in the work of Ozonoff *et al*.[31]

Table 3 Results of the analyses comparing the ALL group with siblings on the four measures of focused attention

Test	ALL mean (n = 19)	Siblings mean (n =19)	Mean (SE) difference	Wilcoxon Z score	p Value
Arithmetic	8.42	9.63	−1.21 (0.65)	−1.89	0.02
Digit span	7.68	9.42	−1.74 (0.54)	−2.66	0.004
Coding	8.79	10.63	−1.84 (0.78)	−2.03	0.04 (two tailed)
Speed of info	48.50	55.44	−6.94 (2.23)	−2.60	0.005

Table 4 Results of the analyses comparing the ALL group with siblings on measures across trials for the VIGIL test

Test	ALL mean (n = 16)	Siblings mean (n = 16)	Mean (SE) difference	Wilcoxon Z score	p Value
Reaction time (ms)	515.37	488.73	26.64 (22.04)	−1.19	0.23
Hit rate	0.79	0.86	−0.06 (0.04)	−1.54	0.12
False alarms	0.11	0.12	−0.01 (0.03)	−0.82	0.41
Commissions	4.01	4.46	−0.45 (1.25)	−0.82	0.41
Omissions	7.57	5.04	2.53 (1.58)	−1.54	0.12

The Wilcoxon matched pairs signed ranks test was used for statistical analysis throughout our study.

Results

The small number of participants in the UKALL VIII group (n = 3) prohibited comparison of the two treatment protocols. However, this was not felt to be of great concern given that all of the participants received the same treatment regimen, which only differed in timing and length of intensification.

THE ABILITY TO FOCUS ATTENTION

There were four measures of the focus element of attention. The arithmetic subtest and digit span subtest of the WISC-R were used to measure focus encode elements, while focus execute elements were measured by means of the coding subtest of the WISC-R and the speed of information processing subtest of the BAS. In light of previous work that has identified deficits in strategic behaviour in children with ALL,[32] we predicted that their performance would be poorer than controls on subtests where a strategic approach would be beneficial, such as the arithmetic and digit span tests. Furthermore, Rodgers and colleagues[32] found that children treated for ALL exhibited slower speed of information processing than controls and we therefore predicted that their performance would be poorer during the speed of information processing subtest. No predictions were possible for performance during the coding subtest. Therefore, all analyses for the focus elements of attention, except coding, were one tailed.

Table 3 gives the results of the analyses comparing the performance of the ALL group with their siblings during the focus tasks.

The leukaemia group gave a significantly poorer performance than the sibling control group on all measures of the focus element of attention.

Table 5 Results of the analyses comparing the ALL group with siblings for each trial of the VIGIL

Test measure	ALL mean	Siblings mean	Mean (SE) difference	Wilcoxon Z score	p Value
Trial 1					
Reaction time (ms)	490.12	474.25	15.87 (22.64)	−0.74	0.46
Commissions	4.12	5.31	−1.18 (1.65)	0.00	1.00
Omissions	5.00	4.25	0.75 (1.48)	−0.16	0.88
Trial 2					
Reaction time (ms)	512.06	496.06	16.0 (30.27)	−0.74	0.46
Commissions	4.00	4.18	−0.18 (1.81)	−0.87	0.38
Omissions	7.06	4.25	2.81 (2.11)	−1.22	0.22
Trial 3					
Reaction time (ms)	530.87	486.06	44.81 (28.52)	−1.82	0.07
Commission	3.31	4.06	−0.75 (1.53)	−0.43	0.67
Omissions	8.43	5.93	2.5 (2.27)	−1.53	0.13
Trial 4					
Reaction time (ms)	528.43	498.56	29.87 (23.41)	−1.28	0.20
Commissions	4.62	4.31	0.31 (1.12)	−0.27	0.78
Omissions	9.68	5.75	3.93 (1.52)	−2.19	0.3

MEASURES OF SUSTAINED ATTENTION

Comparisons were made between participants in the leukaemia group and their sibling controls on the various measures of the VIGIL test of sustained attention. Scores on the VIGIL test were calculated in the following manner:

(1) Hit rate: an overall accuracy of target discrimination, calculated by dividing total number of targets correctly discriminated by total number of targets presented
(2) False alarm: occurs when targets are falsely anticipated and is calculated by dividing the total number of errors of commission by the total number of targets presented
(3) Errors of commission: a frequency measure of incorrect responses
(4) Errors of omission: a frequency measure of number of targets missed
(5) Reaction time: the average time from the presentation of a stimulus to the response.

Technical problems resulted in only 16 of the 19 pairs completing this task. All analyses were two tailed. Table 4 gives the results of these analyses.

Further analysis of performance during the VIGIL task was undertaken by analysing the four trial blocks embedded within the task (table 5). There were no significant differences in performance between participants in the leukaemia group and the control group during any aspects of the VIGIL task.

MEASURES OF ATTENTIONAL SHIFT

We compared scores of the leukaemia group and their matched sibling controls on measures of the WCST, a measure of the shift element of attention. We standardised all scores according to age appropriate norms, with standard scores having a mean of 100 (SD, 15). All analyses were two tailed, with the exception of the comparison of performance on the conceptual level responses, where we predicted that patients with leukaemia would perform worse than sibling controls because of difficulties with the ability to adopt a strategic approach to problem solving.[32] A conceptual level response score was given if three or more responses were given correctly. Table 6 gives the results of these analyses.

No significant differences were found between participants in the leukaemia group and their sibling controls on any measure of the WCST.

Table 6 Results of the analyses comparing performance of the ALL group with sibling controls on measures of the WCST

Test measure	*ALL mean (n = 19)*	*Siblings mean (n = 19)*	*Mean (SE) difference*	*Wilcoxon Z score*	*p Value*
Errors	95.77	104.50	−8.72 (5.86)	−1.28	0.20
Perseverative responses	96.77	100.55	−3.77 (4.38)	−0.96	0.34
Perseverative errors	97.11	103.83	−6.72 (5.26)	−1.37	0.17
Non-perseverative errors	94.88	106.16	−11.27 (6.83)	−1.33	0.18
Conceptual level responses	92.88	102.50	−9.61 (6.32)	−1.18	0.12 (one tailed)

Table 7 Results of the analyses comparing the ALL group with sibling for the categorical data of the WCST

Test measure	*ALL mean (n = 19)*	*Siblings mean (n = 19)*	*Mean (SE) difference*	*Wilcoxon Z score*	*p Value*
Categories completed (n)	1.33	2.11	0.77 (0.78)	−0.73	0.46
Trials to complete first category	1.33	1.16	0.16 (0.27)	−0.55	0.58
Failure to maintain set	1.76	1.11	0.64 (0.36)	−1.68	0.05 (one tailed)
Learning to learn	1.88	1.58	0.29 (0.46)	−0.21	0.83

Four other measures were also yielded from the WCST. All of these measures involved calculating scores and then assigning them to percentile ranges, according to the normative tables (table 7). All analyses were two tailed with the exception of the failure to maintain set category, where we predicted that patients in the leukaemia group would have a significantly poorer performance than sibling controls because of difficulties with appropriate strategy use.[32] The analysis of results revealed that participants in the leukaemia group found it significantly more difficult to maintain set.

Discussion

Our results show a deficient ability to focus attention among the patients treated for ALL when compared with sibling controls; this deficit was apparent in both the focus encode and focus execute elements of attentional ability.

Analysis of performance on the VIGIL test of sustained attention indicates that patients in the leukaemia group performed at comparable levels to their siblings.

Analysis of performance on the WCST shows that children in the ALL group were significantly less able to maintain set than their sibling controls. We advise caution when interpreting these results, given that significance is achieved only because the analysis was one tailed. There are a number of possible explanations for this finding. First, failure to maintain set might reflect inability to benefit from positive feedback provided by the examiner. It may be that, as a consequence of deficits in the focus element of attention, particularly the presence of a decreased speed of information processing, children in the ALL group are impaired in their ability to generate appropriate responses based on the feedback provided. This may have resulted in problems understanding the nature of the task—for example, appreciating the requirement to determine the sorting principle in order to complete it. Instead, the subjects in the ALL group appear to see each card as a separate trial and do not use a systematic approach. Alternatively, failure to maintain set might indicate the presence of difficulties sustaining attention or remaining “on task”. In this case, if subjects experience difficulties concentrating over time it would detract from their ability to approach this task in the required fashion—that is, in maintaining the necessary information over time to produce a consistent response to subsequent trials. This interpretation should be viewed in light of the findings of the VIGIL task, which indicate no deficits in sustained attention for this group.

We included the WCST as a measure of the ability to shift attention from one stimulus to another. An impaired ability to shift attention would be reflected in a high percentage of perseverative errors (and subsequently a high percentage of errors in general). The ALL group showed no significant differences in number of perseverative errors or errors in general when compared with sibling controls. This suggests that ability to shift attention is not impaired for the ALL group. The results support the suggestion that children treated for ALL fail to adopt a systematic approach to problem solving situations

In summary, our results indicate that children who have received treatment for leukaemia have difficulty in focusing attention, and we suggest that many of the focusing difficulties experienced by the ALL group are exacerbated by a decreased speed of information processing. This would mean that more attentional processes are required simply to focus on the central requirements of a task, so fewer resources are available for processing information effectively. Children experiencing these problems would find it difficult to choose effective strategies to aid them in a task and would therefore have difficulty manipulating and organising information in a meaningful and productive way. In addition, results from the WCST suggest that difficulty in focusing attention could result in an inability to respond to external cues and feedback, which could subsequently have an impact on the ability to apply a systematic and methodical approach to problem solving. This implies that the deficits witnessed may have a metacognitive basis, which supports other recent findings.[33 34]

Difficulties with focusing attention will have an impact on academic performance, with the child exhibiting a less planned and strategic approach to cognitive tasks. Of the children who participated in our study, half of those in the leukaemia group were receiving extra tuition at school compared with only one tenth of the sibling controls, with two thirds of the children in the leukaemia group described as experiencing specific difficulties at school, compared with one third of sibling controls. Those who were having extra tuition or specific difficulties reported problems in arithmetic, spelling, and reading.

Problems with focusing attention will inhibit the development of automaticity in calculating basic sums, delaying progress in arithmetic skills. Similarly, deficits in the ability to engage in on line planned, strategic, or metacognitive behaviour, which result from focusing problems, will lead to poor performance in more complex mathematical tasks. Spelling difficulties might be attributable to memory impairments. Difficulties with tasks that require memory skills may result from the impact that attentional difficulties have on the developmental course of memory ability. Reading difficulties could also be affected by memory impairments. Difficulty focusing attention may result in a slow and labourious approach to reading.

The potential importance of our results is that a detailed and comprehensive examination of attentional ability among children treated for ALL may yield information that can be used to develop tools of remediation to target their specific needs. Our study indicates that difficulties at school may result from an inability to focus attention. Some attempts have been made to develop programmes of remediation specifically designed to address the patterns of performance in children treated for ALL, with limited success (J Rodgers, PhD thesis, University of Newcastle upon Tyne, 1992). However, we did not target this specific element of attentional ability. Future attempts at remediation may yield more positive results through the incorporation of activities designed to ameliorate focus difficulties.

We advise caution because of the small sample size and because some children will have experienced frequent absences from school, which may have contributed to their poor performance. However, previous work comparing children with ALL with those who have experienced other forms of cancer indicates that school absenteeism cannot account exclusively for the pattern of cognitive sequelae that seems to be particular to ALL.[35]

All of the children in the ALL group had received 18 Gy CRT and ITMTX as part of their treatment protocol, making it impossible to determine their relative contributions to long term sequelae. Previous studies have attempted to clarify this issue,[36–40] but results have been inconclusive. Furthermore, we cannot predict the long term development of the children involved in our study. Attempts to predict cognitive development as a function of time since treatment are inconclusive; some authors suggest a relatively static picture,[12] while others suggest a decline in ability.[41] Future research should seek answers to these fundamental questions. The introduction of UKALL XI will provide opportunities to determine whether attempts at cognitive intervention should be targeted only at those children who have received radiotherapy, or all children. We believe that until the answers to these questions are forthcoming children who have received treatment for ALL should receive regular intellectual assessments.

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Ethology and cortical visual impairment

In industrialised countries there has been a switch in recent decades from ocular to non-ocular causes of visual impairment. The term cortical visual impairment (CVI) is applied to visual loss arising from defects in the geniculostriate pathways although, by default, other neurological defects may be included. The ophthalmological investigation of CVI is difficult and researchers in Utrecht have enlisted help from their local department of ethology (G Porro and colleagues. *British Journal of Ophthalmology* 1998;**82**:1231–5. See also editorial, pages 1225–6). [The Greek word ethos is variously translated as character, manners, habits, or behaviour. Ethology is, therefore, the study of behaviour in animals and people.]

They studied six girls and three boys aged 19–116 months, all of whom had cerebral palsy, lacked visual contact, had no stable visual fixation, and had defied attempts at visual function assessment. Each was observed by an ethologist for 15 minutes, and responses to visual stimuli were observed and recorded on video. As a result of their observations these workers defined six direct signs (indicative of visual perception) and six indirect signs (regarded as supportive or confirmatory). The direct signs were: intermittent fixation towards the stimulus, looking past it, head movement towards it, following, reaching out, and looking away while reaching. The indirect signs were: avoiding behaviour, posture change, smiling, blinking, facial expression change, and sterotypic behaviour.

More detailed observational studies may improve the understanding of behavioural adaptations to CVI in these children.

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